

10 / 513699

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssptaeal1624

PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * *

NEWS 1 Web Page for STN Seminar Schedule - N. America
NEWS 2 APR 04 STN AnaVist, Version 1, to be discontinued
NEWS 3 APR 15 WPIDS, WPINDEX, and WPIX enhanced with new predefined hit display formats
NEWS 4 APR 28 EMBASE Controlled Term thesaurus enhanced
NEWS 5 APR 28 IMSRESEARCH reloaded with enhancements
NEWS 6 MAY 30 INPAFAMDB now available on STN for patent family searching
NEWS 7 MAY 30 DGENE, PCTGEN, and USGENE enhanced with new homology sequence search option
NEWS 8 JUN 06 EPFULL enhanced with 260,000 English abstracts
NEWS 9 JUN 06 KOREAPAT updated with 41,000 documents
NEWS 10 JUN 13 USPATFULL and USPAT2 updated with 11-character patent numbers for U.S. applications
NEWS 11 JUN 19 CAS REGISTRY includes selected substances from web-based collections
NEWS 12 JUN 25 CA/CAplus and USPAT databases updated with IPC reclassification data
NEWS 13 JUN 30 AEROSPACE enhanced with more than 1 million U.S. patent records
NEWS 14 JUN 30 EMBASE, EMBAL, and LEMBASE updated with additional options to display authors and affiliated organizations
NEWS 15 JUN 30 STN on the Web enhanced with new STN AnaVist Assistant and BLAST plug-in
NEWS 16 JUN 30 STN AnaVist enhanced with database content from EPFULL
NEWS 17 JUL 28 CA/CAplus patent coverage enhanced
NEWS 18 JUL 28 EPFULL enhanced with additional legal status information from the epoline Register
NEWS 19 JUL 28 IFICDB, IFIPAT, and IFIUDB reloaded with enhancements
NEWS 20 JUL 28 STN Viewer performance improved
NEWS 21 AUG 01 INPADOCDB and INPAFAMDB coverage enhanced
NEWS 22 AUG 13 CA/CAplus enhanced with printed Chemical Abstracts page images from 1967-1998
NEWS 23 AUG 15 CAOLD to be discontinued on December 31, 2008
NEWS 24 AUG 15 CAplus currency for Korean patents enhanced
NEWS 25 AUG 25 CA/CAplus, CASREACT, and IFI and USPAT databases enhanced for more flexible patent number searching
NEWS 26 AUG 27 CAS definition of basic patents expanded to ensure comprehensive access to substance and sequence information

10 / 513699

NEWS EXPRESS JUNE 27 08 CURRENT WINDOWS VERSION IS V8.3,
AND CURRENT DISCOVER FILE IS DATED 23 JUNE 2008.

| | |
|------------|---|
| NEWS HOURS | STN Operating Hours Plus Help Desk Availability |
| NEWS LOGIN | Welcome Banner and News Items |
| NEWS IPC8 | For general information regarding STN implementation of IPC 8 |

Enter NEWS followed by the item number or name to see news on that specific topic.

All use of STN is subject to the provisions of the STN Customer agreement. Please note that this agreement limits use to scientific research. Use for software development or design or implementation of commercial gateways or other similar uses is prohibited and may result in loss of user privileges and other penalties.

FILE 'HOME' ENTERED AT 16:01:16 ON 15 SEP 2008

FILE 'REGISTRY' ENTERED AT 16:01:24 ON 15 SEP 2008
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2008 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 14 SEP 2008 HIGHEST RN 1049627-95-3
DICTIONARY FILE UPDATES: 14 SEP 2008 HIGHEST RN 1049627-95-3

New CAS Information Use Policies. enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH July 5, 2008.

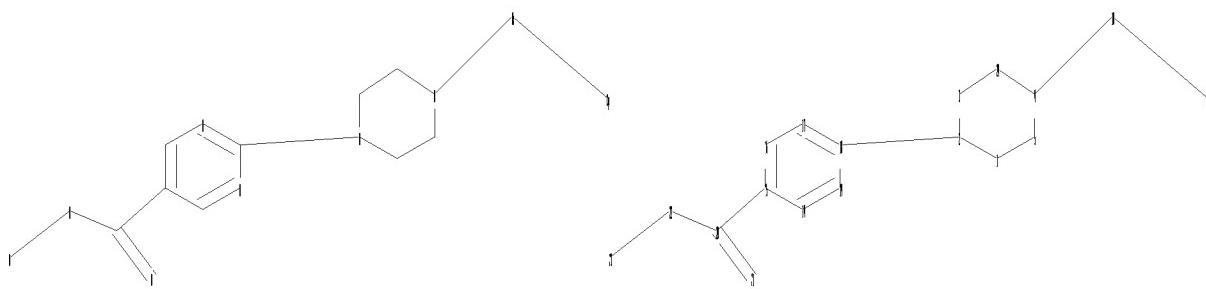
Please note that search-term pricing does apply when conducting Smart SELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/support/stnagen/stndoc/properties.html>

=>
Uploading C:\Program Files\Stnexp\Queries\10506998allow.str

10/513699



chain nodes :

10 11 20 21 22 23

ring nodes :

1 2 3 4 5 14 15 16 17 18 19 24

chain bonds :

2-18 4-10 10-11 15-20 20-21 20-22 22-23

ring bonds :

1-2 1-5 2-3 3-24 4-5 4-24 14-15 14-19 15-16 16-17 17-18 18-19

exact/norm bonds :

1-2 1-5 2-3 2-18 3-24 4-10 4-5 4-24 10-11 20-21 20-22 22-23

exact bonds :

15-20

normalized bonds :

14-15 14-19 15-16 16-17 17-18 18-19

isolated ring systems :

containing 1 :

G1:C,N

G2:Ak,NH2,NO2

G3:O

G4

G5:C,N,Zn,H

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 10:CLASS 11:Atom 14:Atom 15:Atom
16:Atom 17:Atom 18:Atom 19:Atom 20:CLASS 21:CLASS 22:CLASS 23:CLASS 24:Atom

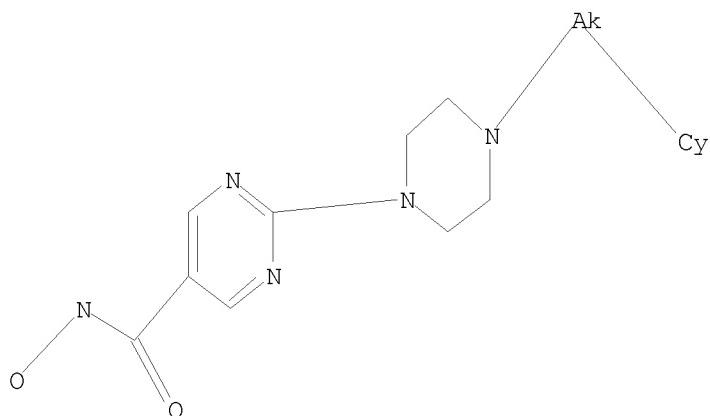
L1 STRUCTURE UPLOADED

=> d 11

L1 HAS NO ANSWERS

L1 STR

10/513699



G1 C, N
G2 Ak, NH2, NO2
G3 O
G4
G5 C, N, Zn, H

Structure attributes must be viewed using STN Express query preparation.

=> s 11 full
FULL SEARCH INITIATED 16:01:46 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 1679 TO ITERATE
100.0% PROCESSED 1679 ITERATIONS 113 ANSWERS
SEARCH TIME: 00.00.01

L2 113 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS SINCE FILE TOTAL
SESSION
FULL ESTIMATED COST 178.36 178.57

FILE 'CAPLUS' ENTERED AT 16:01:51 ON 15 SEP 2008
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2008 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is

10/513699

strictly prohibited.

FILE COVERS 1907 - 15 Sep 2008 VOL 149 ISS 12
FILE LAST UPDATED: 14 Sep 2008 (20080914/ED)

Caplus now includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2008.

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

<http://www.cas.org/legal/infopolicy.html>

=> s l2 full

L3 11 L2

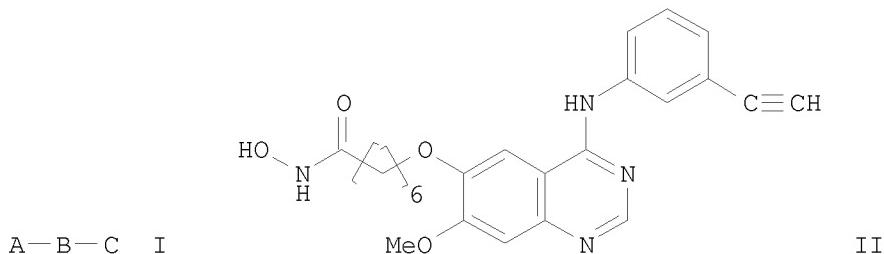
=> d ibib abs hitstr tot

L3 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2008:353001 CAPLUS
DOCUMENT NUMBER: 148:355828
TITLE: Multi-functional small molecules as anti-proliferative agents and their preparation
INVENTOR(S): Cai, Xiong; Qian, Changcheng; Gould, Stephen; Zhai, Haixiao
PATENT ASSIGNEE(S): Curis, Inc., USA
SOURCE: PCT Int. Appl., 494pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|----------|-----------------|------------|
| WO 2008033747 | A2 | 20080320 | WO 2007-US77971 | 20070910 |
| WO 2008033747 | A9 | 20080724 | | |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG,
KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL,
PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | |
| RW: | AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW,
GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA | | | |
| US 20080221132 | A1 | 20080911 | US 2007-852458 | 20070910 |
| PRIORITY APPLN. INFO.: | | | US 2006-843590P | P 20060911 |
| | | | US 2007-895889P | P 20070320 |

OTHER SOURCE(S): MARPAT 148:355828

GI

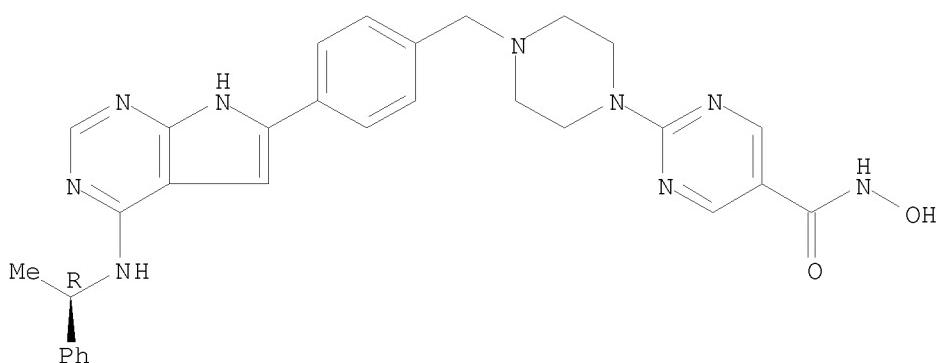


AB The invention relates to the compns., methods, and applications of an approach to selective inhibition of several cellular or mol. targets with a single small mol. More specifically, the present invention relates to multi-functional small mols. of formula I wherein one functionality is capable of inhibiting histone deacetylases (HDAC) and the other functionality is capable of inhibiting a different cellular or mol. pathway involved in aberrant cell proliferation, differentiation or

survival. Compds. of formula I wherein A is a pharmacophore of an anticancer agent capable of inhibiting at least one cellular or mol. pathway involved in the aberrant cell proliferation, differentiation or survival; B is a linker; C is a zinc-binding moiety; and their geometrical isomers, enantiomers, diastereoisomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, are claimed. Example compound II was prepared by a multistep procedure (procedure given). All the invention compds. were evaluated for their antiproliferative activity (some data given).

- IT 1011716-90-7P
 RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRPH (Prophetic); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prophetic starting material; preparation of multi-functional small mols. as antiproliferative agents)
- RN 1011716-90-7 CAPLUS
- CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[4-[(1R)-1-phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.



L3 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN
 ACCESSION NUMBER: 2008:351928 CAPLUS
 DOCUMENT NUMBER: 148:355814
 TITLE: Preparation of (aralkylamino)(phenyl)pyrrolo[2,3-d]pyrimidine derivatives for use as protein tyrosine kinase (PTK) inhibitors
 INVENTOR(S): Cai, Xiong; Qian, Changgeng; Gould, Stephen
 PATENT ASSIGNEE(S): Curis, Inc., USA
 SOURCE: PCT Int. Appl., 123pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2008033745 | A2 | 20080320 | WO 2007-US77968 | 20070910 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| US 20080161320 | A1 | 20080703 | US 2007-852440 | 20070910 |
| PRIORITY APPLN. INFO.: | | | US 2006-843646P | P 20060911 |
| | | | US 2007-895894P | P 20070320 |

OTHER SOURCE(S): MARPAT 148:355814
 GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Fused bicyclic pyrimidine derivs. I and II [Ar = aryl, substituted arylheteroaryl or heteroaryl; Q = absent or (un)substituted alkyl; X = O, S, NH, or aralkylamino; Z = O, S, NR1; Y = N or CR2; B = linker; D = C(O)NH2, NHC(S)CH3, CHC(O)NHacyl, etc.; R1 = H or (un)substituted alkyl; R2 = H, halo, (un)substituted aliphatic, aryl or heteroaryl], and their pharmaceutically acceptable salts, are prepared and disclosed as protein tyrosine kinase (PTK) inhibitors. Thus, e.g., III was prepared by N-alkylation of 1,4-dioxa-8-azaspiro[4.5]decane with 6-(4-(chloromethyl)phenyl)-N-((R)-1-phenylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (preparation given) and deprotection followed by condensation with 6-aminohexanoic acid Me ester and amidation with hydroxylamine. Select I were evaluated in EGFR assays, e.g., III demonstrated an IC50 value of ≤ 0.1 (μ M).

IT 1011716-90-7P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

10/513699

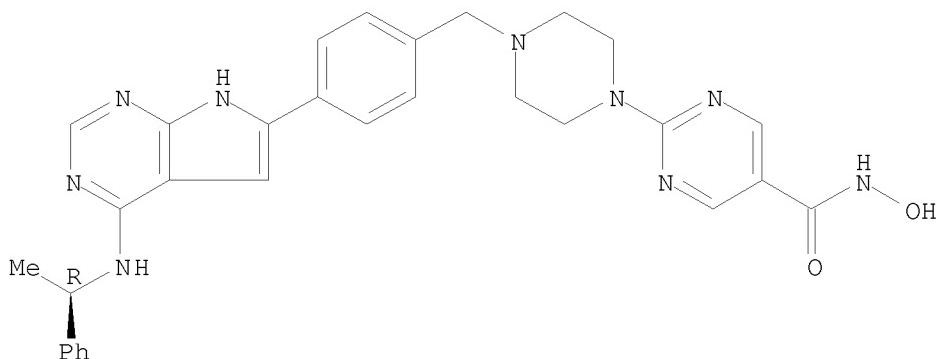
(Uses)

(preparation of (aralkylamino)(phenyl)pyrrolopyrimidine derivs. for use as protein tyrosine kinase (PTK) inhibitors)

RN 1011716-90-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[4-[[4-[(1R)-1-phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

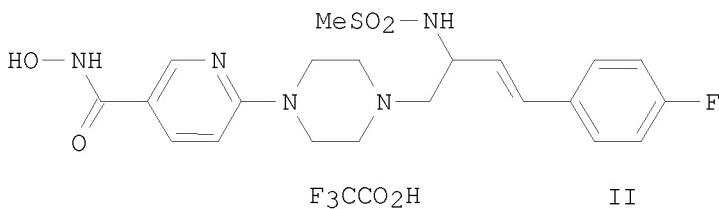
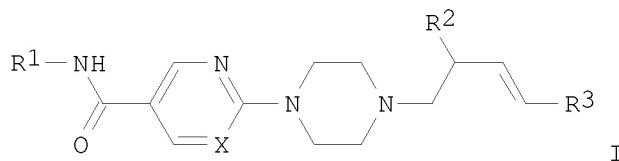
Absolute stereochemistry.



L3 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN
 ACCESSION NUMBER: 2007:816930 CAPLUS
 DOCUMENT NUMBER: 147:211903
 TITLE: Preparation of pyrimidine derivatives as histone deacetylase inhibitors
 INVENTOR(S): Marconnet-Decrane, Laurence Francoise Bernadette; Gaurrand, Sandrine Francoise Dominique; Angibaud, Patrick Rene
 PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.
 SOURCE: PCT Int. Appl., 62pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2007082874 | A1 | 20070726 | WO 2007-EP50371 | 20070116 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN,
KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK,
MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO,
RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT,
TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM | | | | |
| CA 2630717 | A1 | 20070726 | CA 2007-2630717 | 20070116 |
| PRIORITY APPLN. INFO.: | | | EP 2006-100570 | A 20060119 |
| | | | WO 2007-EP50371 | W 20070116 |

OTHER SOURCE(S): MARPAT 147:211903
 GI



AB The title compds. with general formula I [wherein R1 = OH or substituted phenyl; X = N or CH; R2 = amino, alkylamino, alkoxy, OH, etc.; R3 = (un)substituted Ph, naphthalene, or heterocycle] or N-oxide forms, pharmaceutically acceptable salts, or stereoisomeric forms thereof were prepared as histone deacetylase (HDAC) inhibitors for the treatment of proliferative diseases. For example, compound II was prepared in a multi-step synthesis. In vitro assay for inhibition of HDAC was performed to measure the inhibition of HDAC enzymic activity, and colorimetric assay was performed to determine cellular activity on A2780 tumor cells. II showed HDAC inhibitory and anti-proliferative activities in the above two assays with pIC₅₀ values of 7.0 and 5.3, resp. Formulations containing I as active ingredients were also reported.

IT 944738-91-4P 944738-94-7P 944738-97-0P

944739-00-8P 944739-08-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrimidine derivs. as histone deacetylase inhibitors)

RN 944738-91-4 CAPLUS

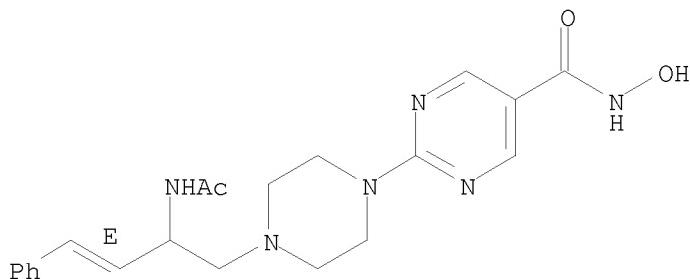
CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(acetylamino)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-90-3

CMF C21 H26 N6 O3

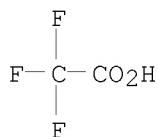
Double bond geometry as shown.



CM 2

CRN 76-05-1

CMF C2 H F3 O2



10/513699

RN 944738-94-7 CAPLUS

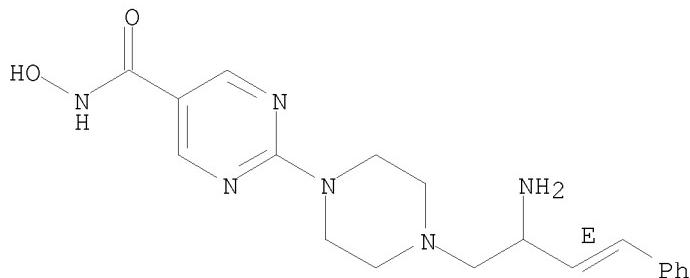
CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-amino-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-93-6

CMF C19 H24 N6 O2

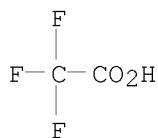
Double bond geometry as shown.



CM 2

CRN 76-05-1

CMF C2 H F3 O2



RN 944738-97-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(2,5-dioxo-1-pyrrolidinyl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

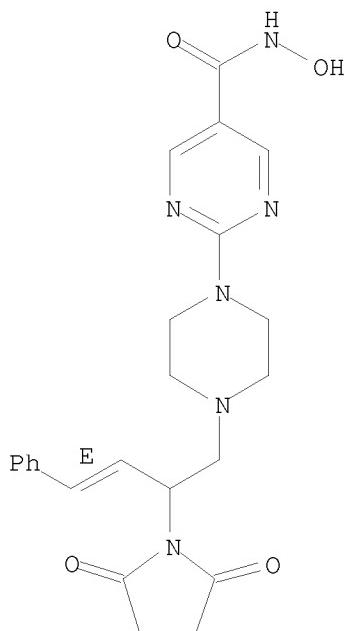
CM 1

CRN 944738-96-9

CMF C23 H26 N6 O4

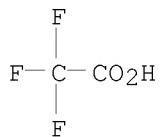
Double bond geometry as shown.

10/513699



CM 2

CRN 76-05-1
CMF C2 H F3 O2



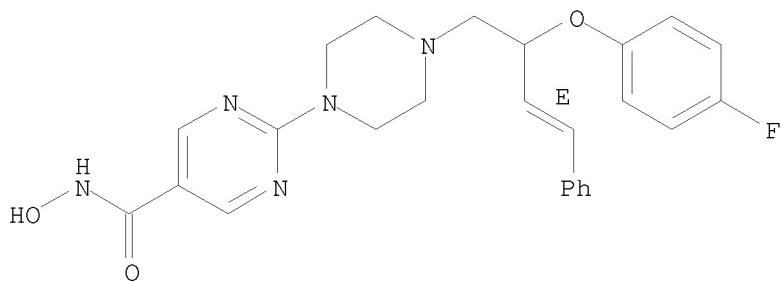
RN 944739-00-8 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(4-fluorophenoxy)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-99-2
CMF C25 H26 F N5 O3

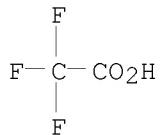
Double bond geometry as shown.

10/513699



CM 2

CRN 76-05-1
CMF C2 H F3 O2

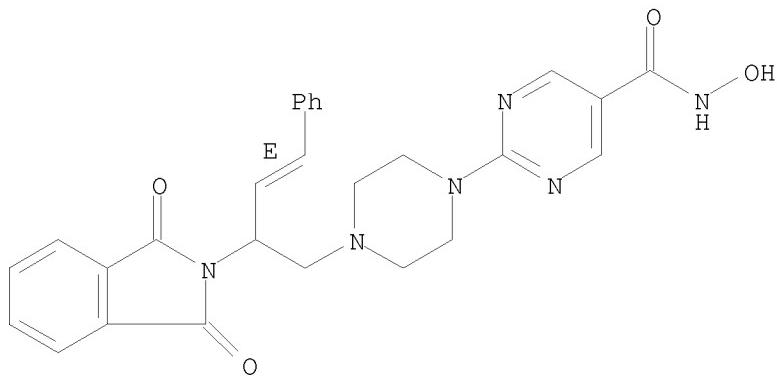


RN 944739-08-6 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-4-phenyl-3-butene-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944739-07-5
CMF C27 H26 N6 O4

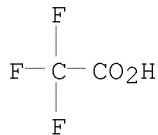
Double bond geometry as shown.



CM 2

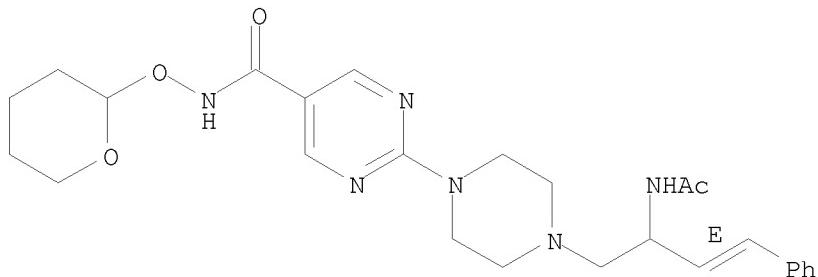
10/513699

CRN 76-05-1
CMF C2 H F3 O2



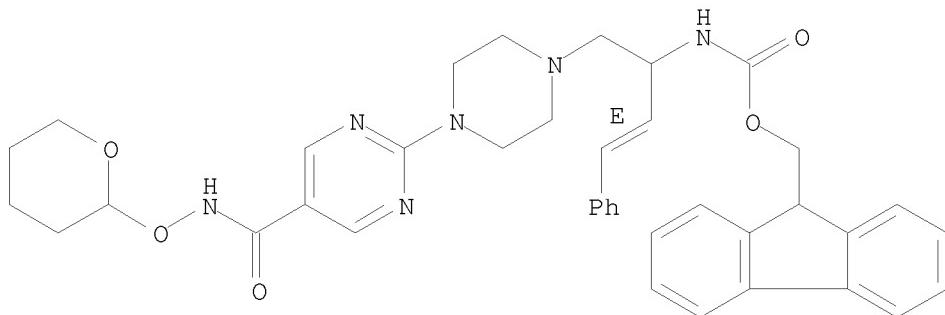
IT 944739-19-9P 944739-25-7P 944739-27-9P
944739-36-0P 944739-42-8P 944739-65-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(preparation of pyrimidine derivs. as histone deacetylase inhibitors)
RN 944739-19-9 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(acetylamino)-4-phenyl-3-buten-1-yl]-
1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

Double bond geometry as shown.



RN 944739-25-7 CAPLUS
CN Carbamic acid, N-[(2E)-3-phenyl-1-[[4-[5-[[[tetrahydro-2H-pyran-2-
yl)oxy]amino]carbonyl]-2-pyrimidinyl]-1-piperazinyl]methyl]-2-propen-1-yl]-
, 9H-fluoren-9-ylmethyl ester (CA INDEX NAME)

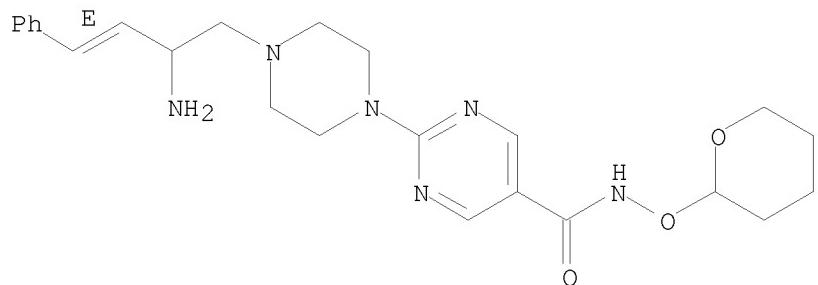
Double bond geometry as shown.



RN 944739-27-9 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-amino-4-phenyl-3-buten-1-yl]-1-
piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

10/513699

Double bond geometry as shown.

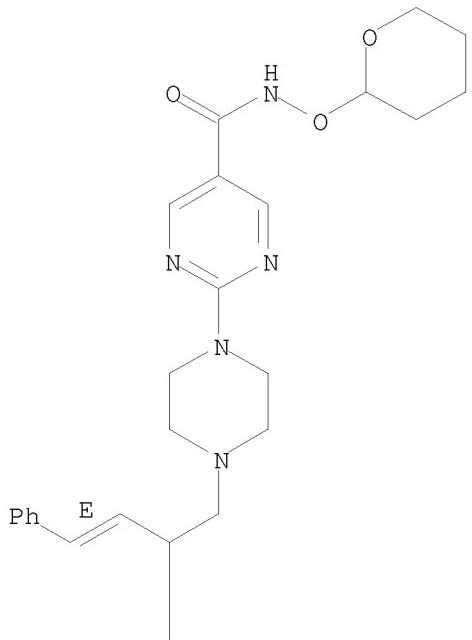


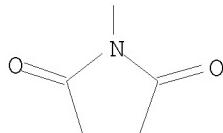
RN 944739-36-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(2,5-dioxo-1-pyrrolidinyl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-[tetrahydro-2H-pyran-2-yl]oxy]- (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A

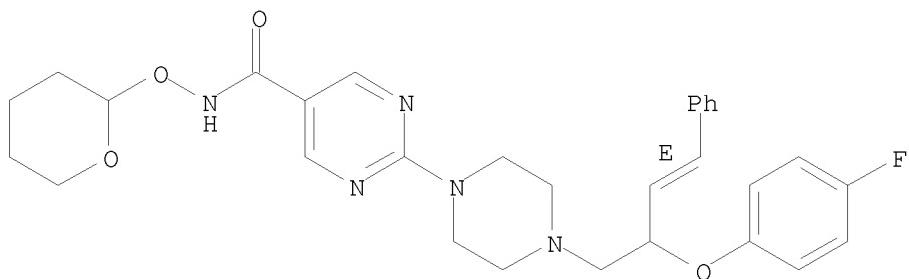




RN 944739-42-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(4-fluorophenoxy)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

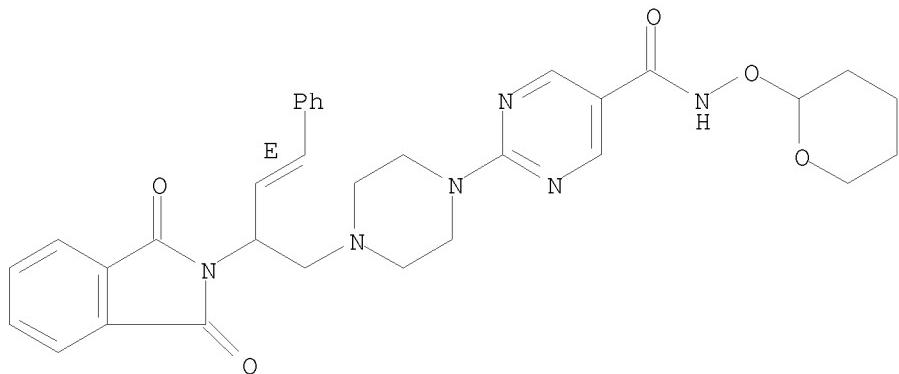
Double bond geometry as shown.



RN 944739-65-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT:

4

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/513699

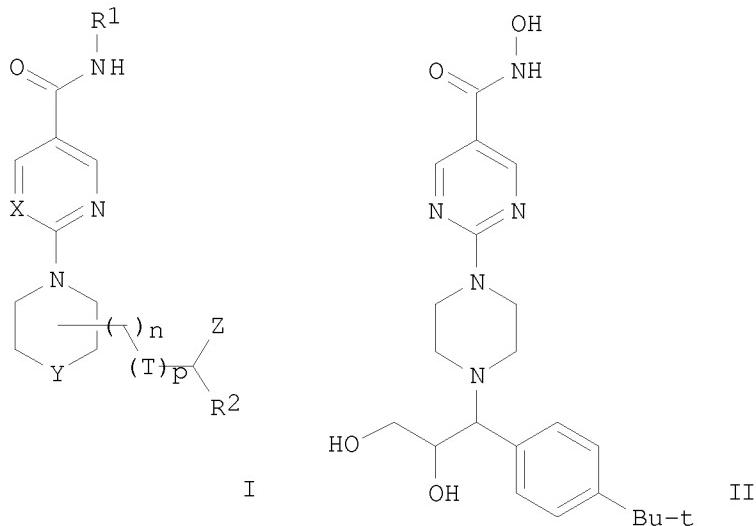
L3 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:816806 CAPLUS
DOCUMENT NUMBER: 147:211902
TITLE: Preparation of pyrimidine derivatives as histone deacetylase inhibitors
INVENTOR(S): Angibaud, Patrick Rene; Van Brandt, Sven Franciscus Anna; Marconnet-Decrane, Laurence Francoise Bernadette; Roux, Bruno
PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.
SOURCE: PCT Int. Appl., 63pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2007082880 | A1 | 20070726 | WO 2007-EP50379 | 20070116 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |

PRIORITY APPLN. INFO.: EP 2006-100571 A 20060119

OTHER SOURCE(S): MARPAT 147:211902

GI



AB The title compds. with general formula I [wherein R1 = OH or substituted phenyl; R2 = -CH₂OH, -CH₂OCH₃, -CH₂OCH₂CH₃, or -CH₂CH(OH)CH₂OH; T = N(R₃), where R₃ = H, alkyl, cycloalkyl, etc.; X = N or CH; Y = O, NH, CH₂, etc.; n = 0-1; p = 0-1, provided that when p = 0 then n = 0 and Y = N, and -CH(R₂)-Z is attached to Y; Z = (un)substituted aryl or heteroaryl] or N-oxide forms, pharmaceutically acceptable salts, or stereoisomeric forms thereof were prepared as histone deacetylase (HDAC) inhibitors for the treatment of proliferative diseases. For example, compound II was prepared in a multi-step synthesis. In vitro assay for inhibition of HDAC was performed to measure the inhibition of HDAC enzymic activity, and colorimetric assay was performed to determine cellular activity on A2780 tumor cells. II showed HDAC inhibitory and anti-proliferative activities in the above two assays with pIC₅₀ values of 7.0 and 7.1, resp. Formulations containing I as active ingredients were also reported.

IT 944712-03-2P 944712-05-4P 944712-07-6P
944712-09-8P 944712-10-1P 944712-12-3P

944712-14-5P 944712-16-7P 944712-18-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrimidine derivs. as histone deacetylase inhibitors)

RN 944712-03-2 CAPLUS

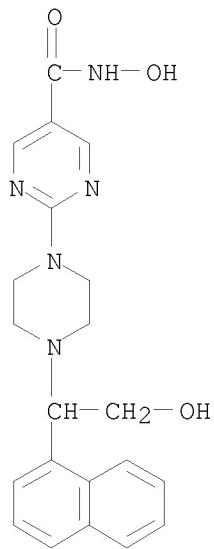
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-(1-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-02-1

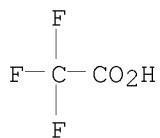
CMF C21 H23 N5 O3

10/513699



CM 2

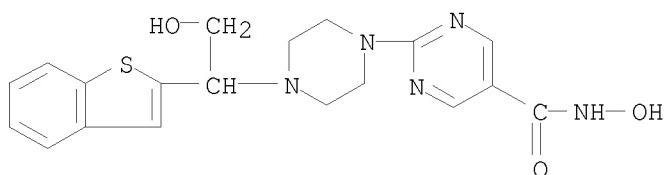
CRN 76-05-1
CMF C2 H F3 O2



RN 944712-05-4 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-(1-benzo[b]thien-2-yl-2-hydroxyethyl)-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

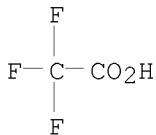
CRN 944712-04-3
CMF C19 H21 N5 O3 S



CM 2

10/513699

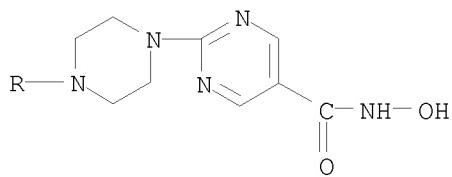
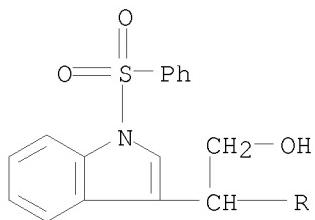
CRN 76-05-1
CMF C2 H F3 O2



RN 944712-07-6 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-[1-(phenylsulfonyl)-1H-indol-3-yl]ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

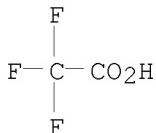
CM 1

CRN 944712-06-5
CMF C25 H26 N6 O5 S



CM 2

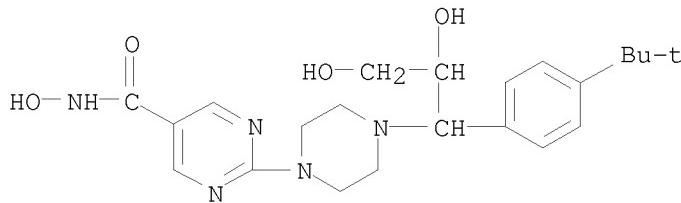
CRN 76-05-1
CMF C2 H F3 O2



RN 944712-09-8 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[1-[4-(1,1-dimethylethyl)phenyl]-2,3-

10/513699

dihydroxypropyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



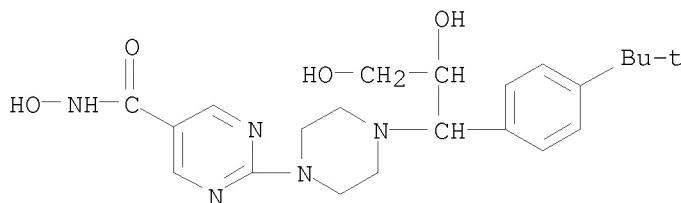
RN 944712-10-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1)
(CA INDEX NAME)

CM 1

CRN 944712-09-8

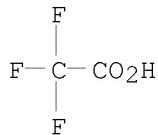
CMF C22 H31 N5 O4



CM 2

CRN 76-05-1

CMF C2 H F3 O2



RN 944712-12-3 CAPLUS

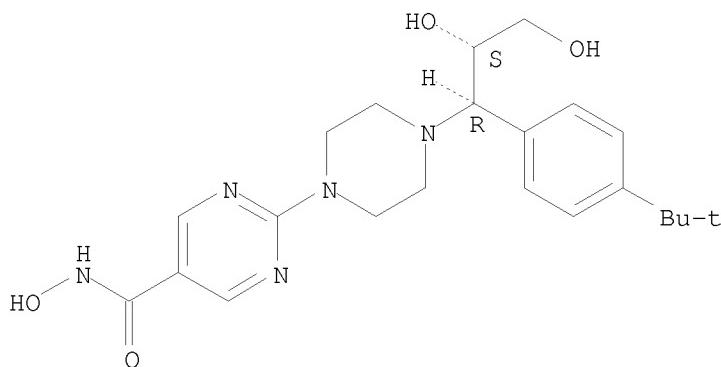
CN 5-Pyrimidinecarboxamide, 2-[4-[(1R,2S)-1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?)
(CA INDEX NAME)

CM 1

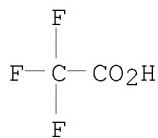
CRN 944712-11-2

CMF C22 H31 N5 O4

Absolute stereochemistry.

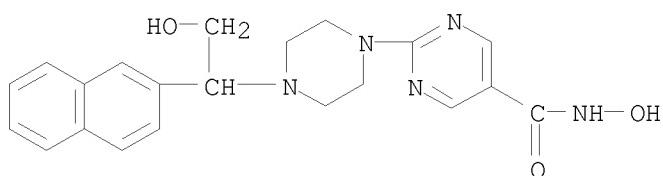


CM 2

CRN 76-05-1
CMF C2 H F3 O2

RN 944712-14-5 CAPLUS
 CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-(2-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

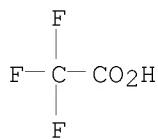
CM 1

CRN 944712-13-4
CMF C21 H23 N5 O3

CM 2

CRN 76-05-1
CMF C2 H F3 O2

10/513699



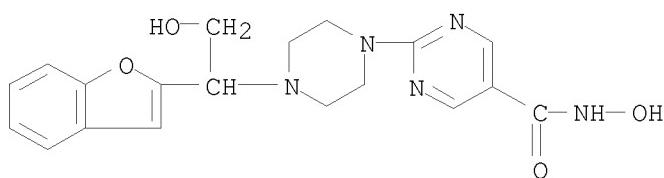
RN 944712-16-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-(2-benzofuranyl)-2-hydroxyethyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-15-6

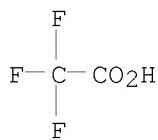
CMF C19 H21 N5 O4



CM 2

CRN 76-05-1

CMF C2 H F3 O2



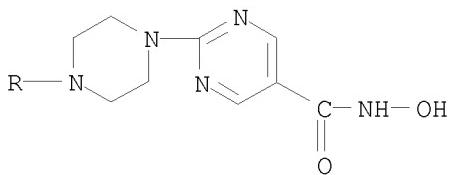
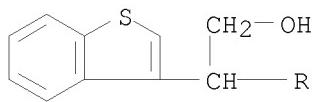
RN 944712-18-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(1-benzo[b]thien-3-yl-2-hydroxyethyl)-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-17-8

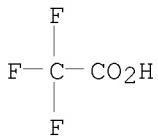
CMF C19 H21 N5 O3 S



CM 2

CRN 76-05-1

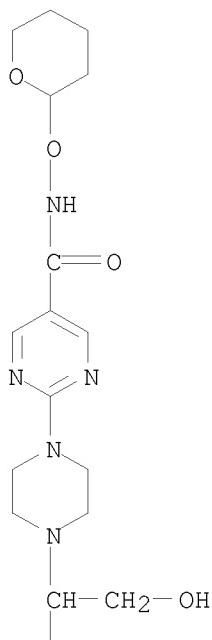
CMF C2 H F3 O2

IT 944712-19-0P 944712-20-3P 944712-23-6P
944712-27-0P 944712-30-5PRL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(preparation of pyrimidine derivs. as histone deacetylase inhibitors)

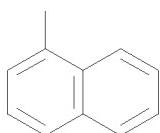
RN 944712-19-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-hydroxy-1-(1-naphthalenyl)ethyl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

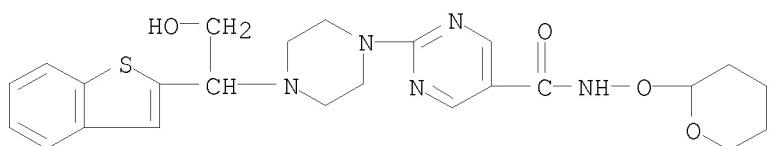
PAGE 1-A



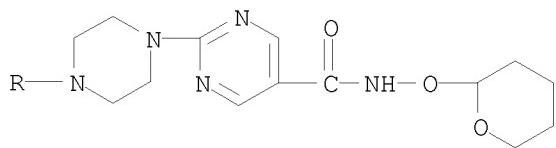
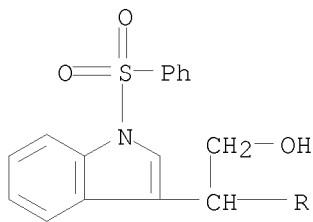
PAGE 2-A



RN 944712-20-3 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-(1-benzo[b]thien-2-yl-2-hydroxyethyl)-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

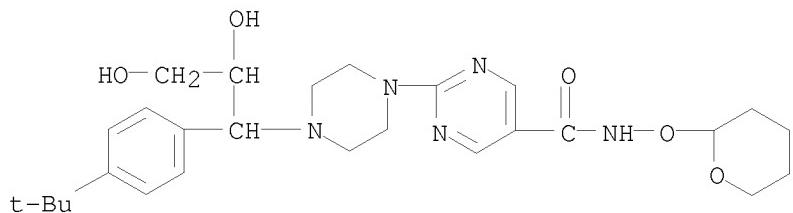


RN 944712-23-6 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[2-hydroxy-1-[1-(phenylsulfonyl)-1H-indol-3-yl]ethyl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)



RN 944712-27-0 CAPLUS

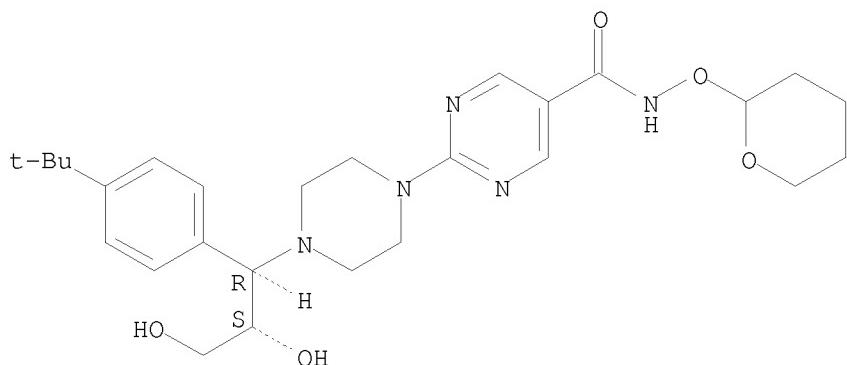
CN 5-Pyrimidinecarboxamide, 2-[4-[1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)



RN 944712-30-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R,2S)-1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

Absolute stereochemistry.



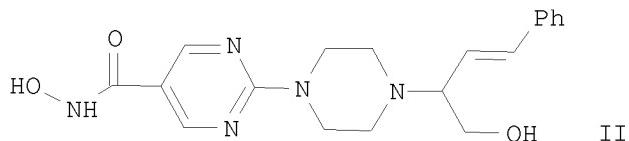
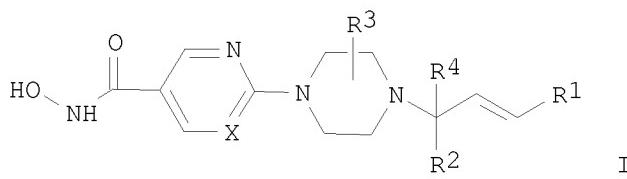
10/513699

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN
 ACCESSION NUMBER: 2006:101446 CAPLUS
 DOCUMENT NUMBER: 144:192266
 TITLE: Preparation of substituted propenyl piperazine derivatives as novel inhibitors of histone deacetylase
 INVENTOR(S): Van Brandt, Sven Franciscus Anna; Van Emelen, Kristof; Angibaud, Patrick Rene; Marconnet-Decrane, Laurence Francoise Bernadette; Arts, Janine
 PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.
 SOURCE: PCT Int. Appl., 67 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|------------|
| WO 2006010749 | A2 | 20060202 | WO 2005-EP53611 | 20050725 |
| WO 2006010749 | A3 | 20060608 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| AU 2005266311 | A1 | 20060202 | AU 2005-266311 | 20050725 |
| CA 2572971 | A1 | 20060202 | CA 2005-2572971 | 20050725 |
| EP 1776358 | A2 | 20070425 | EP 2005-777776 | 20050725 |
| R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU | | | | |
| CN 1993356 | A | 20070704 | CN 2005-80025487 | 20050725 |
| JP 2008508234 | T | 20080321 | JP 2007-523072 | 20050725 |
| BR 2005013891 | A | 20080520 | BR 2005-13891 | 20050725 |
| KR 2007043978 | A | 20070426 | KR 2007-701641 | 20070123 |
| US 20070135424 | A1 | 20070614 | US 2007-626215 | 20070123 |
| IN 2007DN00658 | A | 20070803 | IN 2007-DN658 | 20070124 |
| MX 200701119 | A | 20070315 | MX 2007-1119 | 20070126 |
| NO 2007001117 | A | 20070227 | NO 2007-1117 | 20070227 |
| PRIORITY APPLN. INFO.: | | | EP 2004-77171 | A 20040728 |
| | | | US 2004-592357P | P 20040729 |
| | | | WO 2005-EP53611 | W 20050725 |

OTHER SOURCE(S): CASREACT 144:192266; MARPAT 144:192266
 GI



AB Substituted propenyl piperazine derivs. I, wherein X is independently N or CH; R1 is Ph, naphthalenyl or heterocyclyl; wherein each of said Ph or naphthalenyl is optionally substituted with one or two substituents each independently selected from halo, alkyl, alkyloxy, poly-halo-alkyl, aryl, hydroxy, cyano, amino, alkylcarbonylamino, alkylsulfonylamino, hydroxycarbonyl, alkyloxycarbonyl, hydroxyalkyl, alkyloxymethyl, aminomethyl, alkylaminomethyl, alkylcarbonylaminomethyl, alkylsulfonylaminomethyl, aminosulfonyl, alkylaminosulfonyl or heterocyclyl; R2 is hydrogen, -CH₂R₅, trifluoromethyl, -C(O)-R₆, or -CH-NR₇R₈; wherein each R₅ is independently hydrogen, hydroxy, alkyloxy, alkyloxyalkyloxy, alkylcarbonyloxy, piperazinyl, N-methylpiperazinyl, morpholinyl, thiomorpholinyl, imidazolyl or triazolyl; each R₆ is independently hydroxy, alkyloxy, amino or mono- or di(alkyl)amino, cycloalkylamino, hydroxyalkylamino, piperazinyl, N-methylpiperazinyl, morpholinyl or thiomorpholinyl; each R₇ and R₈ are independently hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, or mono- or di(alkyl)aminosulfonyl; R₃ is hydrogen, hydroxymethyl, aminomethyl or mono- or di(alkyl)aminomethyl; R₄ is hydrogen or alkyl; were prepared and having histone deacetylase inhibiting enzymic activity and to inhibit proliferative conditions, such as cancer and psoriasis. Thus, propenyl piperazine derivative II was prepared and tested in vitro and in nude mice as inhibitor of histone deacetylase and was better than R306465 after oral administration. P21 enzyme linked immunosorbent assay has been applied to determine the p21 protein expression level in human A2780 ovarian carcinoma cells. In vitro assay for inhibition of histone deacetylase is reported. P21 induction was measured as the consequence of DNA damage or as the consequence of histone deacetylase inhibition. Antiproliferative activity of title compds. was determined on A2780 cells (neg. log value of the IC₅₀, pIC₅₀ = 7.9-8.2).

IT 875138-85-5P 875138-87-7P 875138-88-8P
 875138-89-9P 875138-90-2P 875138-91-3P
 875138-93-5P 875138-94-6P 875138-98-0P
 875139-00-7P 875139-02-9P 875139-04-1P
 875139-06-3P 875139-07-4P 875139-09-6P
 875139-11-0P 875139-13-2P 875139-14-3P
 875139-15-4P 875139-17-6P 875139-19-8P
 875139-20-1P 875139-21-2P 875139-23-4P
 875139-24-5P 875139-25-6P 875139-26-7P
 875139-27-8P 875139-28-9P 875139-29-0P
 875139-30-3P 875139-31-4P 875139-69-8P

10/513699

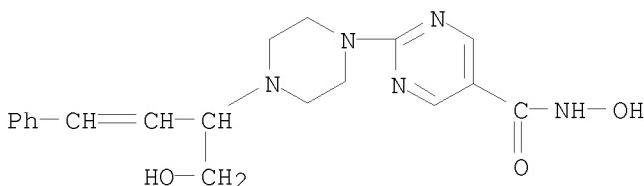
875139-70-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of substituted propenyl piperazine derivs. as novel inhibitors of histone deacetylase)

RN 875138-85-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)



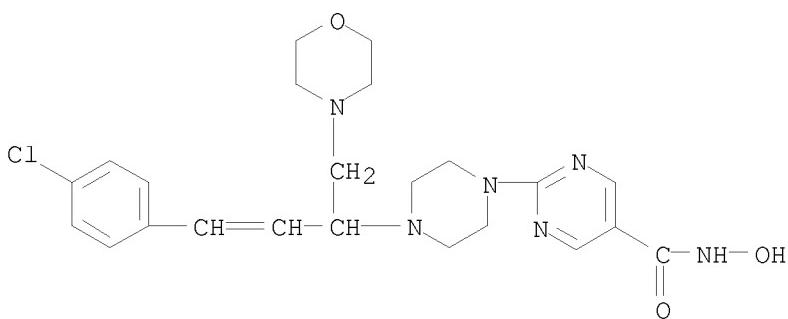
RN 875138-87-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-chlorophenyl)-1-(4-morpholinylmethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-86-6

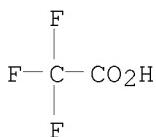
CMF C23 H29 Cl N6 O3



CM 2

CRN 76-05-1

CMF C2 H F3 O2

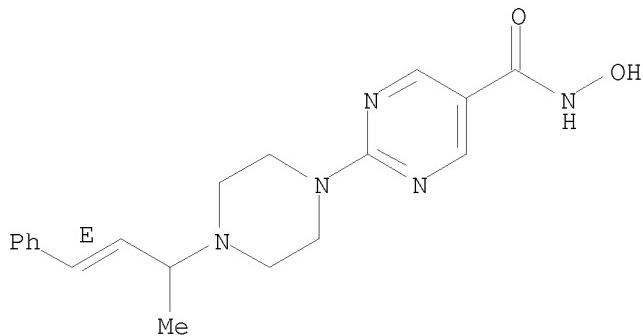


10/513699

RN 875138-88-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-methyl-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Double bond geometry as shown.



RN 875138-89-9 CAPLUS

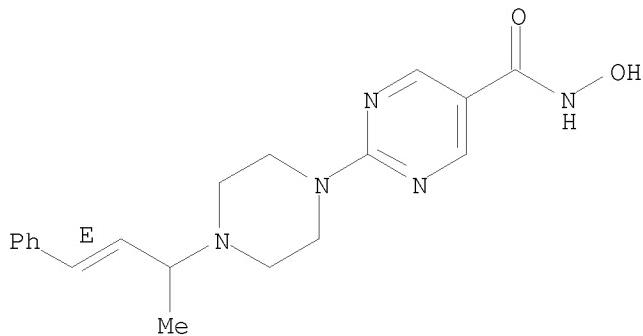
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-methyl-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-88-8

CMF C19 H23 N5 O2

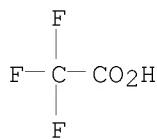
Double bond geometry as shown.



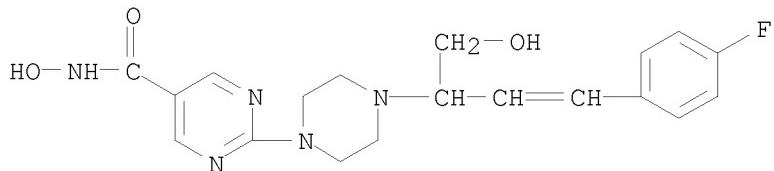
CM 2

CRN 76-05-1

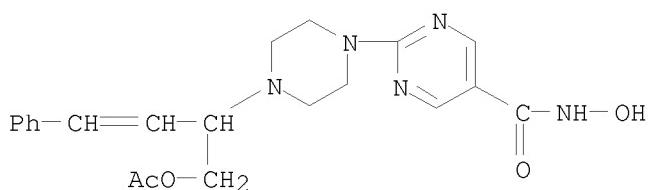
CMF C2 H F3 O2



RN 875138-90-2 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



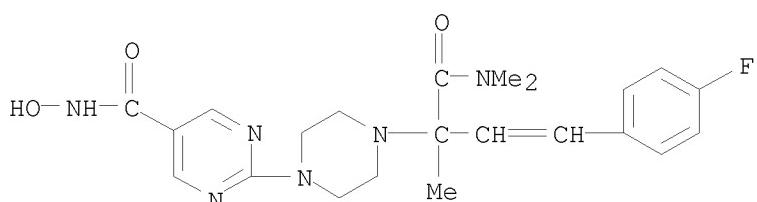
RN 875138-91-3 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(acetyloxy)methyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



RN 875138-93-5 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(dimethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

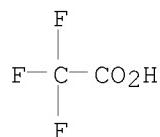
CRN 875138-92-4
 CMF C22 H27 F N6 O3



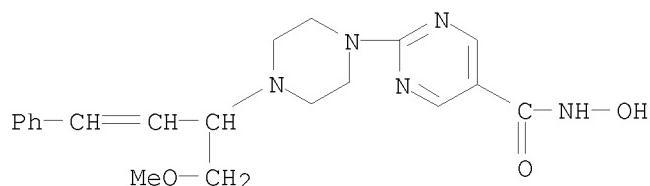
CM 2

10/513699

CRN 76-05-1
CMF C2 H F3 O2



RN 875138-94-6 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(methoxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

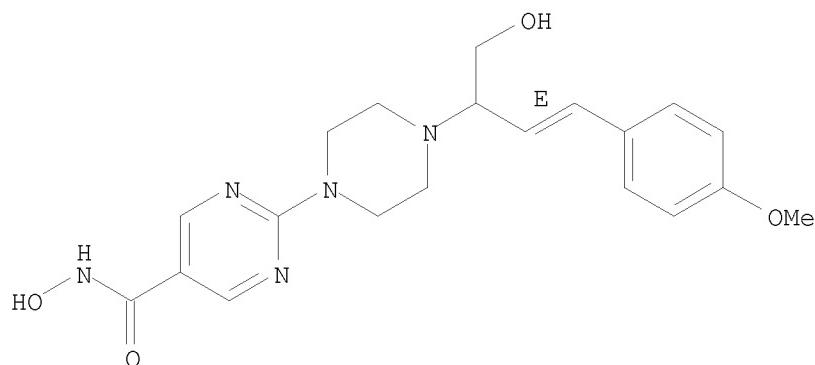


RN 875138-98-0 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-(hydroxymethyl)-3-(4-methoxyphenyl)-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-97-9
CMF C20 H25 N5 O4

Double bond geometry as shown.

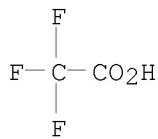


CM 2

CRN 76-05-1

10/513699

CMF C2 H F3 O2



RN 875139-00-7 CAPLUS

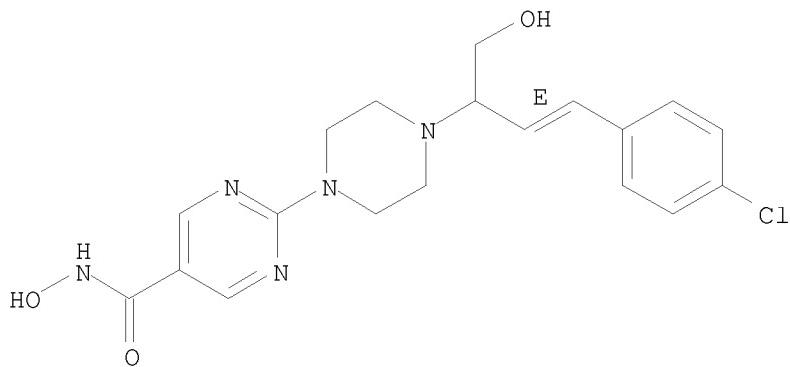
CN 5-Pyrimidinecarboxamide, 2-[4-[(2E)-3-(4-chlorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-99-1

CMF C19 H22 Cl N5 O3

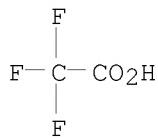
Double bond geometry as shown.



CM 2

CRN 76-05-1

CMF C2 H F3 O2



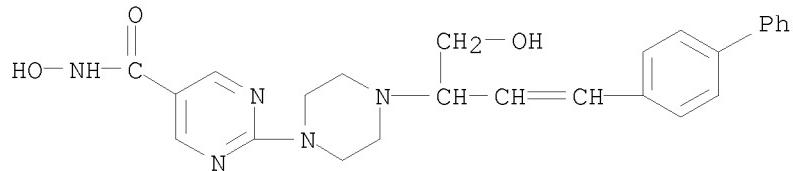
RN 875139-02-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-[1,1'-biphenyl]-4-yl-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

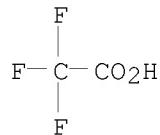
10/513699

CRN 875139-01-8
CMF C25 H27 N5 O3



CM 2

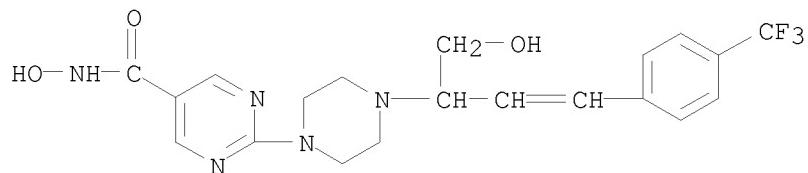
CRN 76-05-1
CMF C2 H F3 O2



RN 875139-04-1 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(hydroxymethyl)-3-[4-(trifluoromethyl)phenyl]-2-propen-1-yl]piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

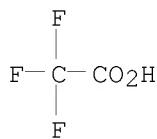
CRN 875139-03-0
CMF C20 H22 F3 N5 O3



CM 2

CRN 76-05-1
CMF C2 H F3 O2

10/513699



RN 875139-06-3 CAPLUS

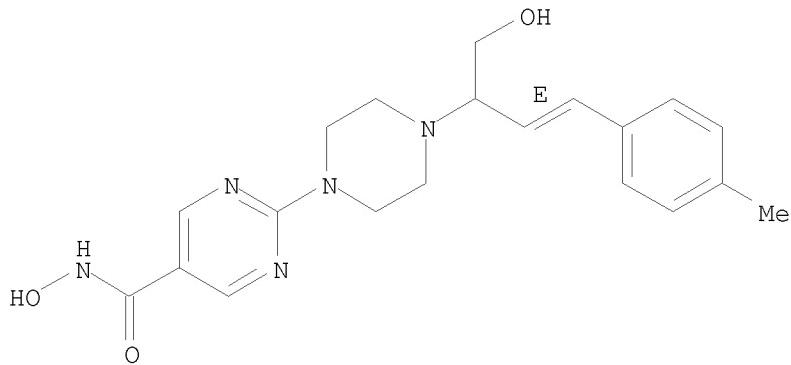
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-(hydroxymethyl)-3-(4-methylphenyl)-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-05-2

CMF C20 H25 N5 O3

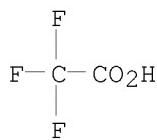
Double bond geometry as shown.



CM 2

CRN 76-05-1

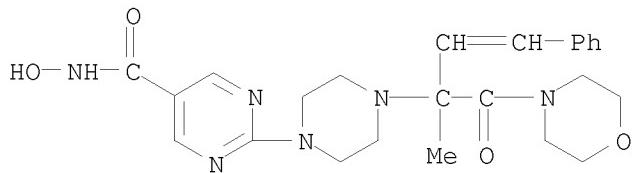
CMF C2 H F3 O2



RN 875139-07-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(1-methyl-1-(4-morpholinylcarbonyl)-3-phenyl-2-propen-1-yl)-1-piperazinyl]- (CA INDEX NAME)

10/513699



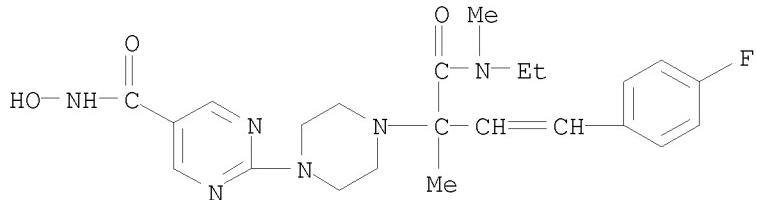
RN 875139-09-6 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(ethylmethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-08-5

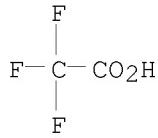
CMF C23 H29 F N6 O3



CM 2

CRN 76-05-1

CMF C2 H F3 O2



RN 875139-11-0 CAPLUS

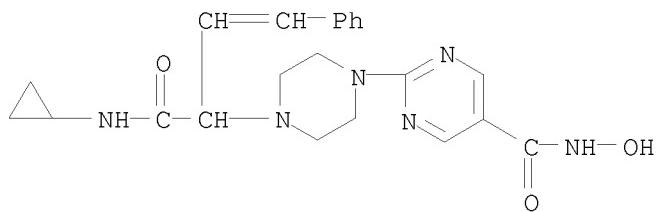
CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(cyclopropylamino)carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-10-9

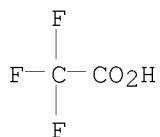
CMF C22 H26 N6 O3

10/513699



CM 2

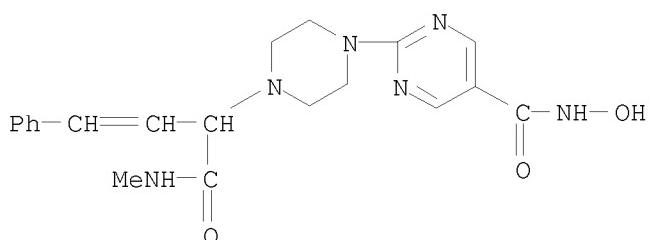
CRN 76-05-1
CMF C2 H F3 O2



RN 875139-13-2 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-[(methylamino)carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

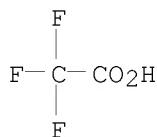
CRN 875139-12-1
CMF C20 H24 N6 O3



CM 2

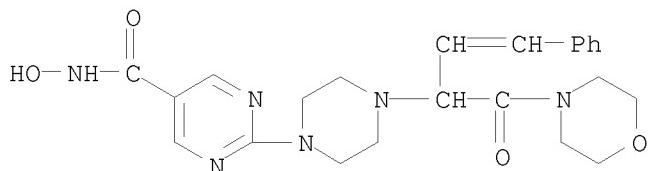
CRN 76-05-1
CMF C2 H F3 O2

10/513699



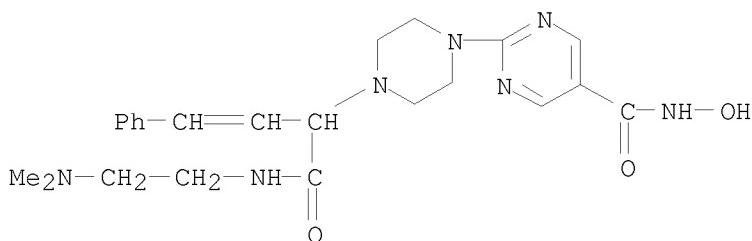
RN 875139-14-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(4-morpholinylcarbonyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)



RN 875139-15-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[[2-(dimethylamino)ethyl]amino]carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl-N-hydroxy- (CA INDEX NAME)



RN 875139-17-6 CAPLUS

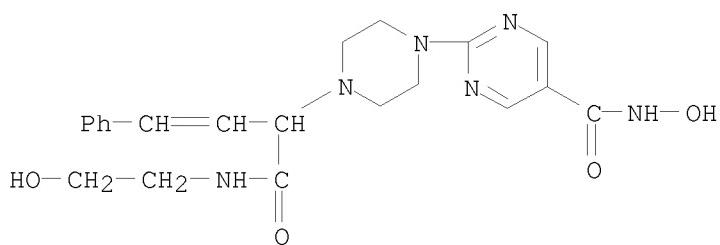
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-[(2-hydroxyethyl)amino]carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-16-5

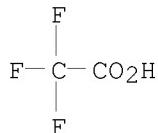
CMF C21 H26 N6 O4

10/513699



CM 2

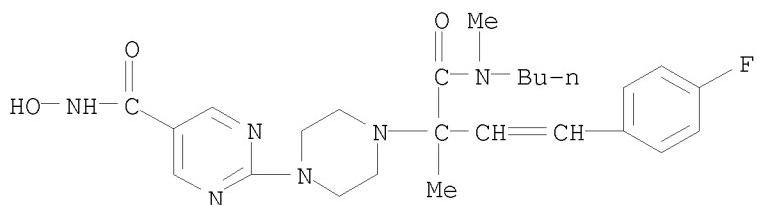
CRN 76-05-1
CMF C2 H F3 O2



RN 875139-19-8 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[(butylmethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

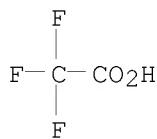
CRN 875139-18-7
CMF C25 H33 F N6 O3



CM 2

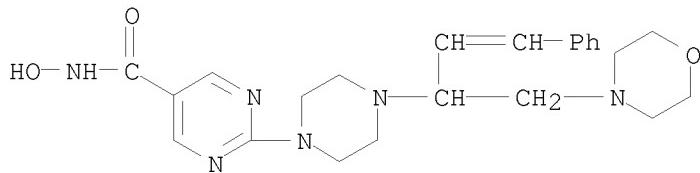
CRN 76-05-1
CMF C2 H F3 O2

10/513699



RN 875139-20-1 CAPLUS

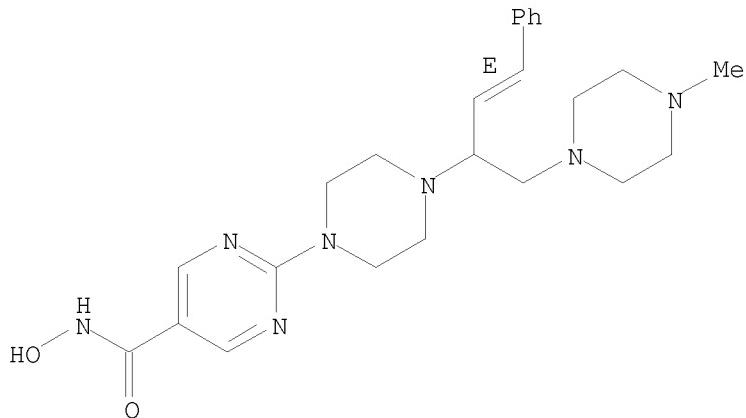
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(4-morpholinylmethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)



RN 875139-21-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[((2E)-1-[(4-methyl-1-piperazinyl)methyl]-3-phenyl-2-propen-1-yl)-1-piperazinyl]- (CA INDEX NAME)

Double bond geometry as shown.



RN 875139-23-4 CAPLUS

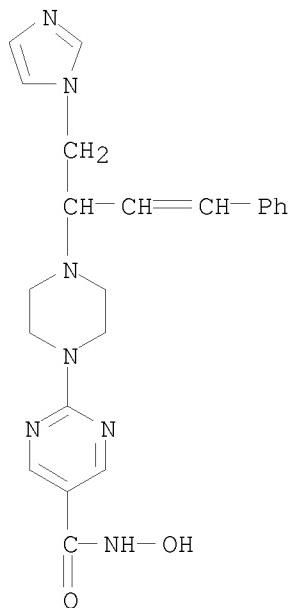
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(1H-imidazol-1-ylmethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-22-3

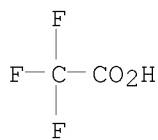
CMF C22 H25 N7 O2

10/513699

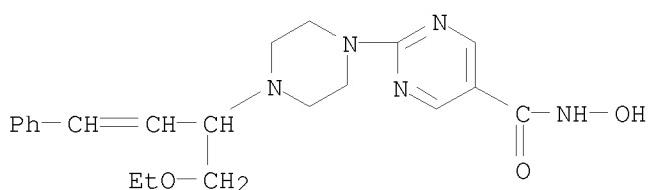


CM 2

CRN 76-05-1
CMF C2 H F3 O2



RN 875139-24-5 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[1-(ethoxymethyl)-3-phenyl-2-propenyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

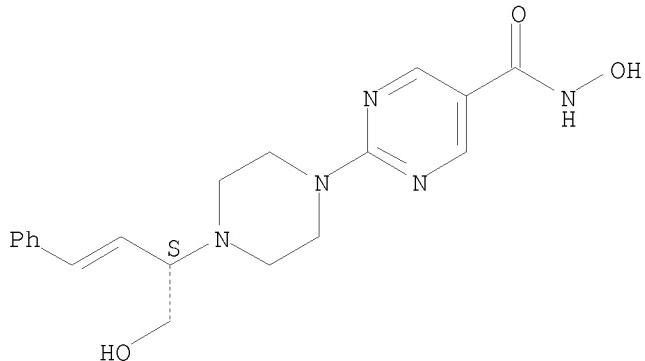


RN 875139-25-6 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(1S)-1-(hydroxymethyl)-3-phenyl-2-propenyl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

10/513699

Double bond geometry unknown.

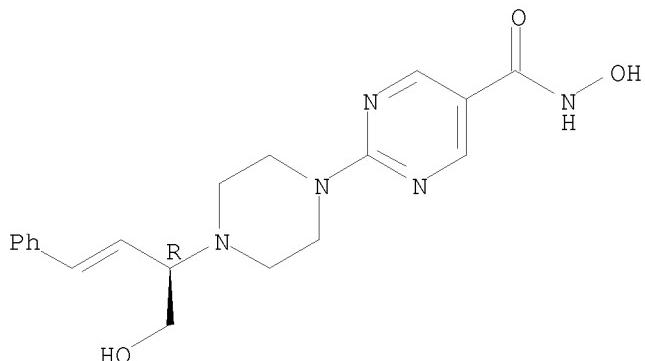


RN 875139-26-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(1R)-1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

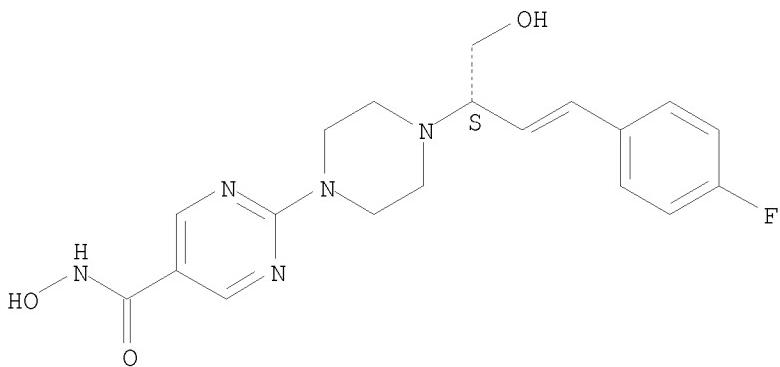


RN 875139-27-8 CAPLUS

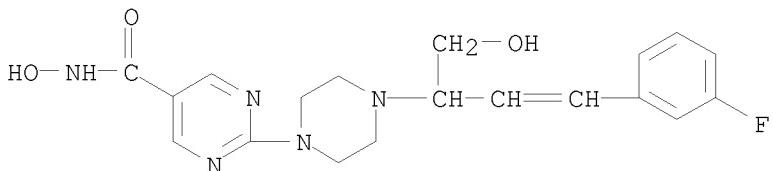
CN 5-Pyrimidinecarboxamide, 2-[4-[(1S)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.

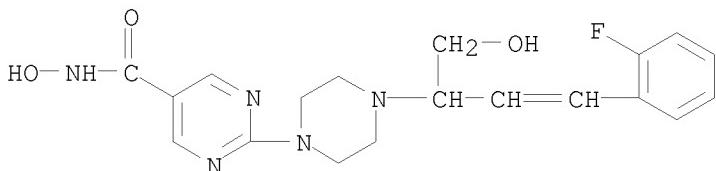
Double bond geometry unknown.



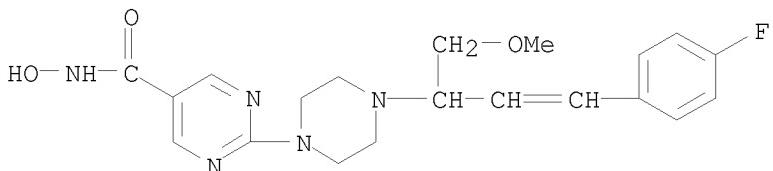
RN 875139-28-9 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[3-(3-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



RN 875139-29-0 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[3-(2-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



RN 875139-30-3 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-fluorophenyl)-1-(methoxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

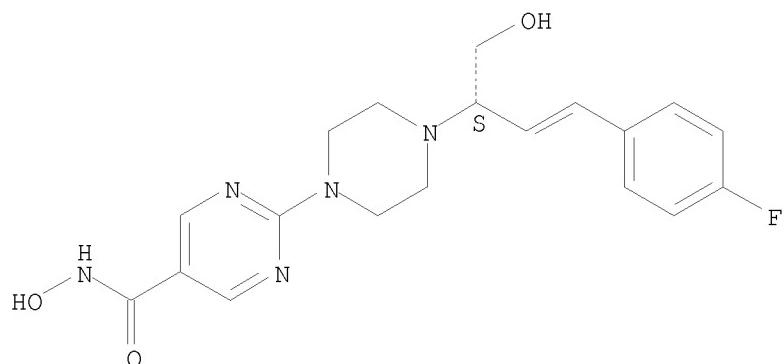


RN 875139-31-4 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-fluorophenyl)-1-(hydroxymethyl)-2-

10/513699

propen-1-yl]-1-piperazinyl]-N-hydroxy-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

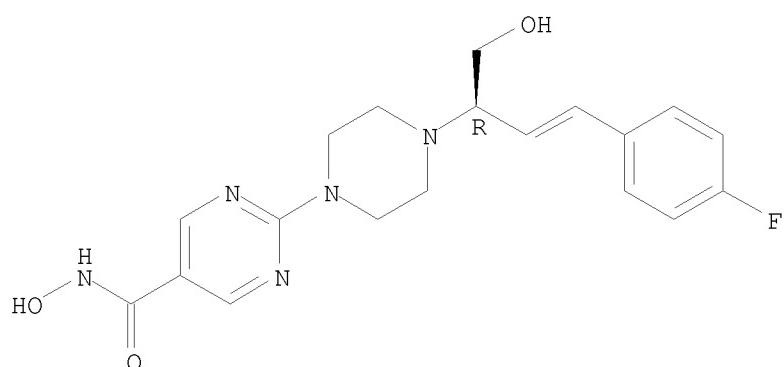


● HCl

RN 875139-69-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

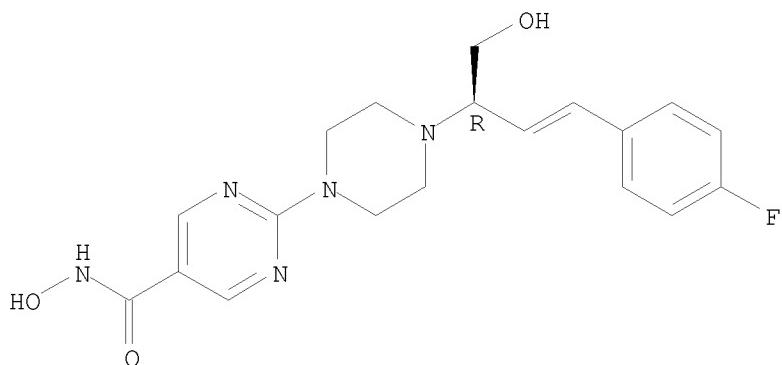
Absolute stereochemistry.
Double bond geometry unknown.



RN 875139-70-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



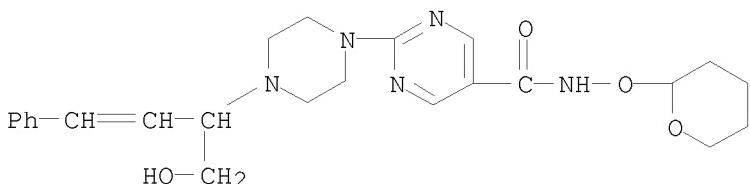
● HCl

IT 875138-54-8P 875138-59-3P 875138-62-8P
875138-66-2P 875138-70-8P 875138-73-1P
875138-77-5P 875138-78-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of substituted propenyl piperazine derivs. as novel inhibitors of histone deacetylase)

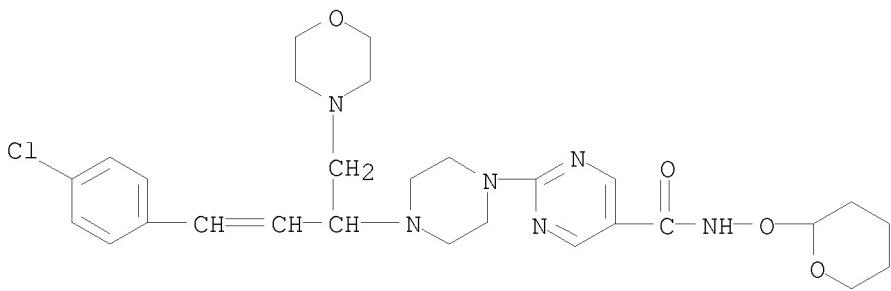
RN 875138-54-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)



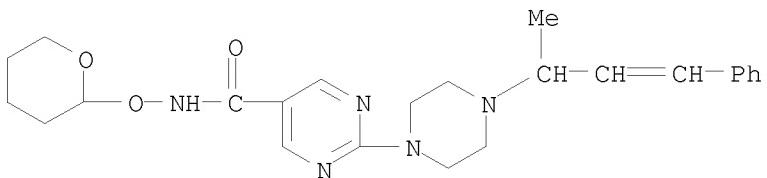
RN 875138-59-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-chlorophenyl)-1-(4-morpholinylmethyl)-2-propen-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)



RN 875138-62-8 CAPLUS

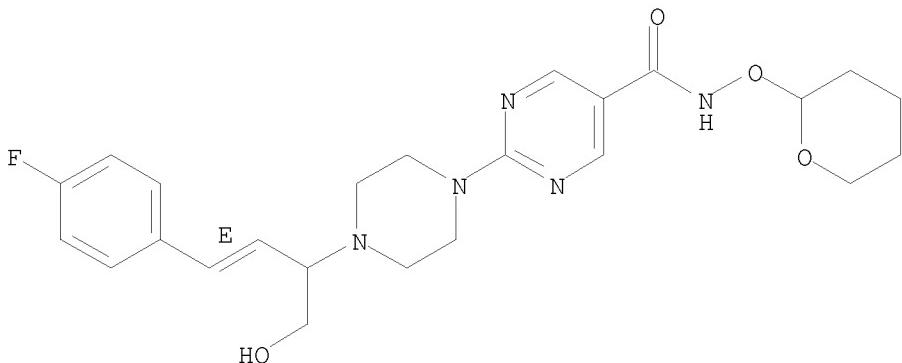
CN 5-Pyrimidinecarboxamide, 2-[4-(1-methyl-3-phenyl-2-propen-1-yl)-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)



RN 875138-66-2 CAPLUS

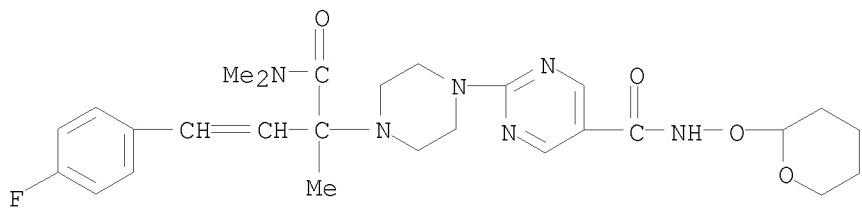
CN 5-Pyrimidinecarboxamide, 2-[4-[(2E)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

Double bond geometry as shown.

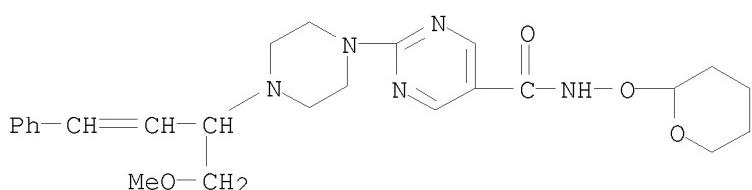


RN 875138-70-8 CAPLUS

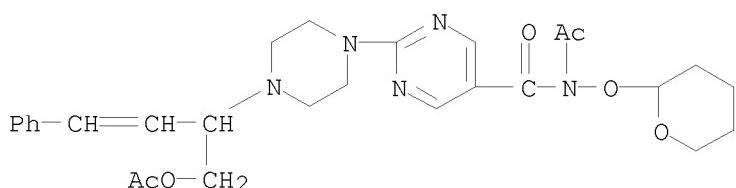
CN 5-Pyrimidinecarboxamide, 2-[4-[(1R)-1-(dimethylamino)-2-hydroxyethyl]-1-methyl-2-propenyl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)



RN 875138-73-1 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[1-(methoxymethyl)-3-phenyl-2-propenyl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)



RN 875138-77-5 CAPLUS
 CN 5-Pyrimidinecarboxamide, N-acetyl-2-[4-[1-[(acetyloxy)methyl]-3-phenyl-2-propenyl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

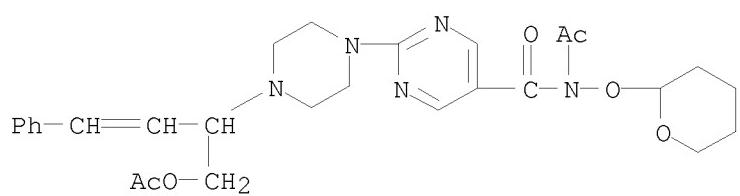


RN 875138-78-6 CAPLUS
 CN 5-Pyrimidinecarboxamide, N-acetyl-2-[4-[1-[(acetyloxy)methyl]-3-phenyl-2-propenyl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]-, ethanedioate (1:1) (CA INDEX NAME)

CM 1

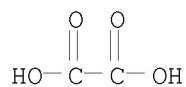
CRN 875138-77-5
 CMF C28 H35 N5 O6

10/513699



CM 2

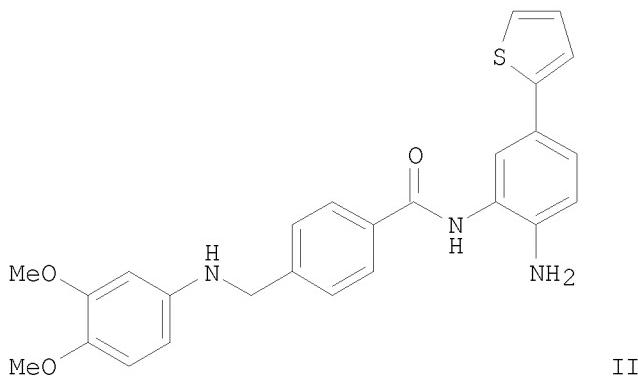
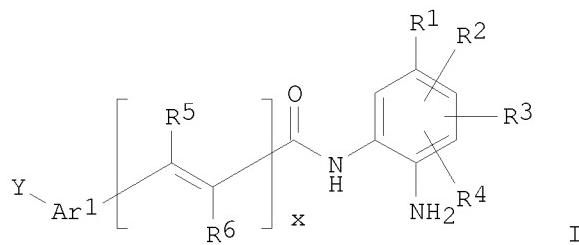
CRN 144-62-7
CMF C2 H2 O4



10/513699

L3 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:300395 CAPLUS
DOCUMENT NUMBER: 142:355054
TITLE: Preparation of amide derivatives as inhibitors of histone deacetylase
INVENTOR(S): Moradei, Oscar; Paquin, Isabelle; Leit, Silvana;
Frechette, Sylvie; Vaisburg, Arkadii; Besterman,
Jeffrey M.; Tessier, Pierre; Mallais, Tammy C.
PATENT ASSIGNEE(S): Methylgene, Inc., Can.
SOURCE: PCT Int. Appl., 559 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|--|----------|------------------|-------------|
| WO 2005030705 | A1 | 20050407 | WO 2004-US31591 | 20040924 |
| WO 2005030705 | A9 | 20060420 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG | | | | |
| AU 2004276337 | A1 | 20050407 | AU 2004-276337 | 20040924 |
| CA 2539117 | A1 | 20050407 | CA 2004-2539117 | 20040924 |
| EP 1663953 | A1 | 20060607 | EP 2004-789074 | 20040924 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR | | | | |
| CN 1882529 | A | 20061220 | CN 2004-80034571 | 20040924 |
| JP 2007506785 | T | 20070322 | JP 2006-528279 | 20040924 |
| US 20080132459 | A1 | 20080605 | US 2006-574088 | 20060323 |
| JP 2008094847 | A | 20080424 | JP 2007-281356 | 20071030 |
| PRIORITY APPLN. INFO.: | | | US 2003-505884P | P 20030924 |
| | | | US 2003-532973P | P 20031229 |
| | | | US 2004-561082P | P 20040409 |
| | | | JP 2006-528279 | A3 20040924 |
| | | | WO 2004-US31591 | W 20040924 |
| OTHER SOURCE(S): GI | CASREACT 142:355054; MARPAT 142:355054 | | | |



AB Title compds. I [Ar1 = (un)saturated-, (un)substituted-mono or fused poly-cyclic hydrocarbyl optionally containing 1-4 heteroatoms per ring; R1 = (un)substituted-mono-, -bi-, -tri-cyclic-aryl or -heteroaryl; R2, R3, and R4 independently = H, halo, amino, etc.; R5 and R6 independently = H, alkyl, aryl, etc.; x = 0-1; Y = any pharmaceutically acceptable chemical moiety consisting of 1 to 50 atoms with provisions] and their pharmaceutically acceptable salts, are prepared and disclosed as inhibitors of histone deacetylase. Thus, e.g., II was prepared by Suzuki coupling of 2-bromo-2-nitro-phenylamine (preparation given) with 2-thiopheneboronic acid followed by carbonylation with 4-[3,4-dimethoxy-(phenylamino)-methyl]benzoic acid (preparation given) and subsequent reduction. The inhibitory

capability of I towards antiproliferative activity of histone deacetylase enzyme was evaluated using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay and it revealed that certain compds. of the invention had MTT IC₅₀ values in the range of below 1 up to 20 μM. I as histone deacetylase inhibitors should prove useful in the treatment of diseases such as, but not limited to, cell proliferative disease, protozoal disease, and fungal disease.

IT 603985-86-0P 603985-88-2P 603985-90-6P

603985-94-0P 603991-95-3P 603991-96-4P

603992-24-1P 603992-25-2P 603992-26-3P

603992-27-4P 603992-28-5P 604784-81-8P

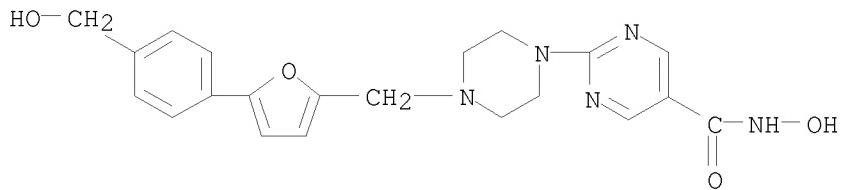
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of amide derivs. as inhibitors of histone deacetylase)

RN 603985-86-0 CAPLUS

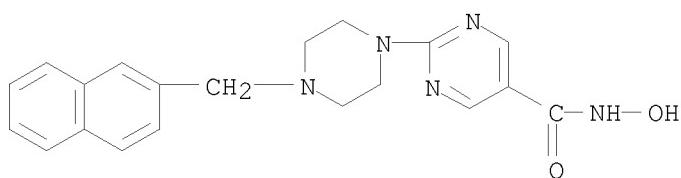
10/513699

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl- (CA INDEX NAME)



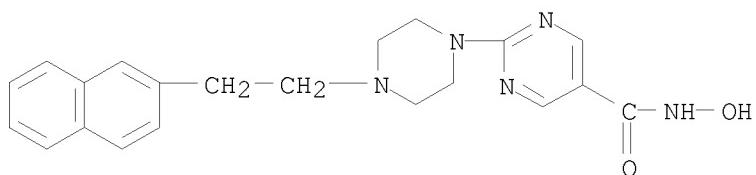
RN 603985-88-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl- (CA INDEX NAME)



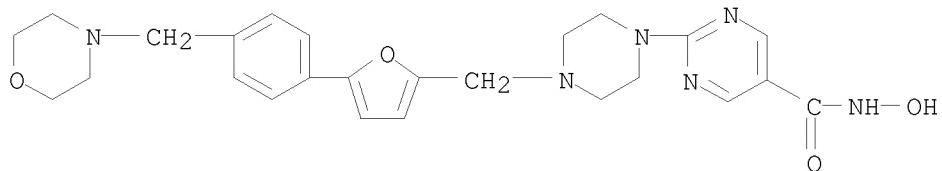
RN 603985-90-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl- (CA INDEX NAME)



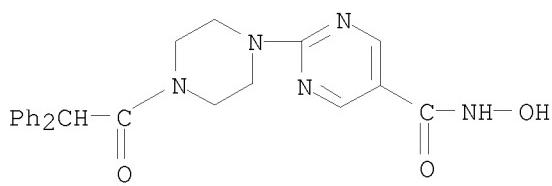
RN 603985-94-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl- (CA INDEX NAME)



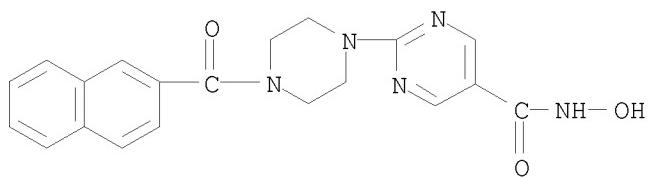
RN 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



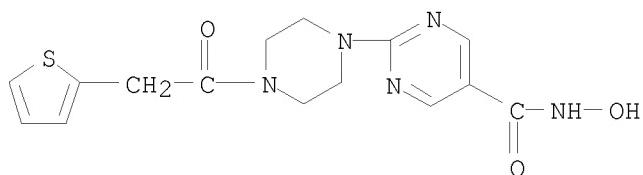
RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



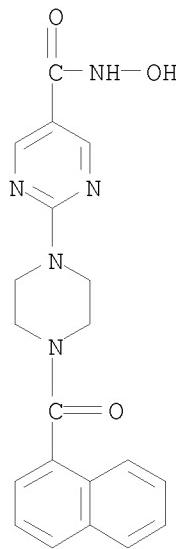
RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)



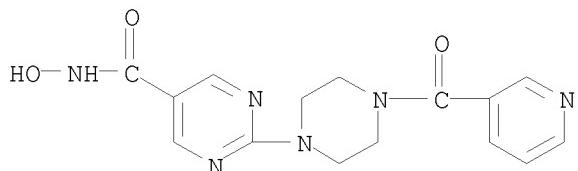
RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



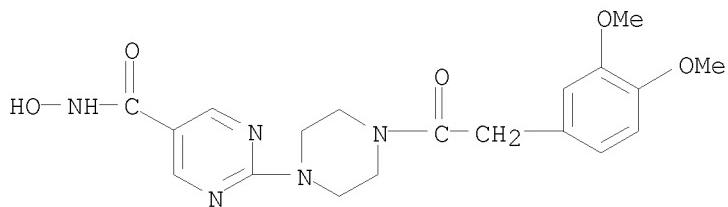
RN 603992-26-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



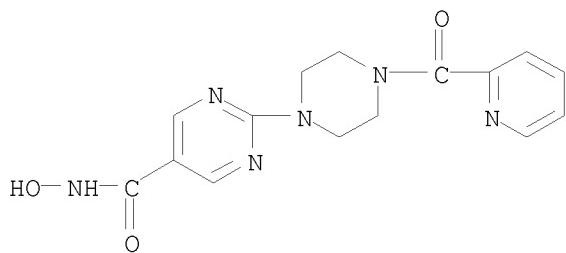
RN 603992-27-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



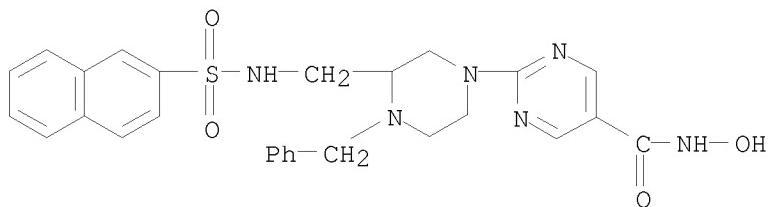
RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



RN 604784-81-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[3-[(2-naphthalenylsulfonyl)amino]methoxy]-4-(phenylmethyl)-1-piperazinyl- (CA INDEX NAME)



REFERENCE COUNT:

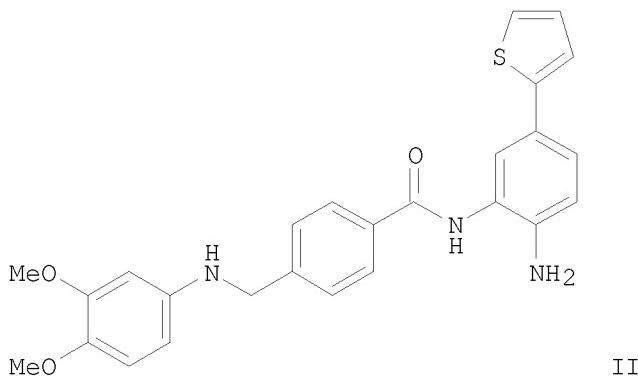
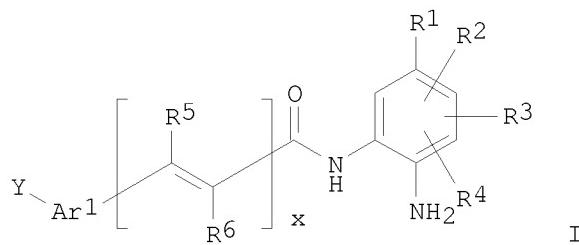
6

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/513699

L3 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:300394 CAPLUS
DOCUMENT NUMBER: 142:373563
TITLE: Preparation of amide derivatives as inhibitors of histone deacetylase
INVENTOR(S): Moradei, Oscar; Paquin, Isabelle; Leit, Silvana;
Frechette, Sylvie; Vaisburg, Arkadii; Besterman,
Jeffrey M.; Tessier, Pierre; Mallais, Tammy C.
PATENT ASSIGNEE(S): Methylgene, Inc., Can.
SOURCE: PCT Int. Appl., 389 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|--|---|---|
| WO 2005030704 | A1 | 20050407 | WO 2004-US31590 | 20040924 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG | | | | |
| JP 2008094847 | A | 20080424 | JP 2007-281356
US 2003-505884P
US 2003-532973P
US 2004-561082P
JP 2006-528279 | 20071030
P 20030924
P 20031229
P 20040409
A3 20040924 |
| PRIORITY APPLN. INFO.: | | | | |
| OTHER SOURCE(S): GI | | CASREACT 142:373563; MARPAT 142:373563 | | |



AB Title compds. I [Ar1 = (un)saturated-, (un)substituted-mono or fused poly-cyclic hydrocarbyl optionally containing 1-4 heteroatoms per ring; R1 = (un)substituted-mono-, -bi-, -tri-cyclic-aryl or -heteroaryl; R2, R3, and R4 independently = H, halo, amino, etc.; R5 and R6 independently = H, alkyl, aryl, etc.; x = 0-1; Y = any pharmaceutically acceptable chemical moiety consisting of 1 to 50 atoms with provisions] and their pharmaceutically acceptable salts, are prepared and disclosed as inhibitors of histone deacetylase. Thus, e.g., II was prepared by Suzuki coupling of 2-bromo-2-nitro-phenylamine (preparation given) with 2-thiopheneboronic acid followed by carbonylation with 4-[3,4-dimethoxy-(phenylamino)-methyl]benzoic acid (preparation given) and subsequent reduction. The inhibitory

capability of I towards antiproliferative activity of histone deacetylase enzyme was evaluated using 3-[4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium] bromide (MTT) assay and it revealed that certain compds. of the invention had MTT IC₅₀ values in the range of below 1 up to 20 μM. I as histone deacetylase inhibitors should prove useful in the treatment of diseases such as, but not limited to, cell proliferative disease, protozoal disease, and fungal disease.

IT 603985-86-0P 603985-88-2P 603985-90-6P

603985-94-0P 603991-95-3P 603991-96-4P

603992-24-1P 603992-25-2P 603992-26-3P

603992-27-4P 603992-28-5P 604784-81-8P

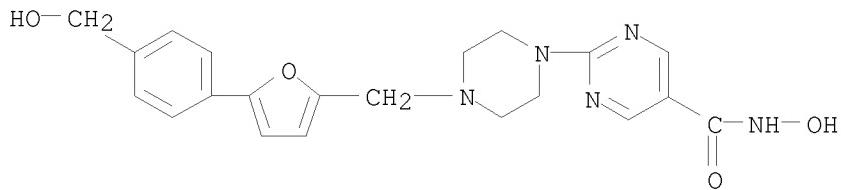
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of amide derivs. as inhibitors of histone deacetylase)

RN 603985-86-0 CAPLUS

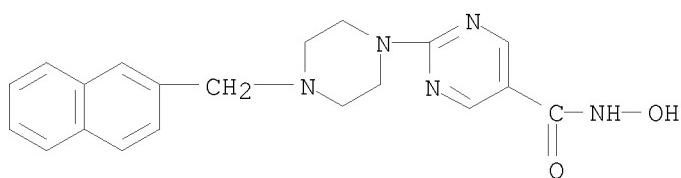
10/513699

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl- (CA INDEX NAME)



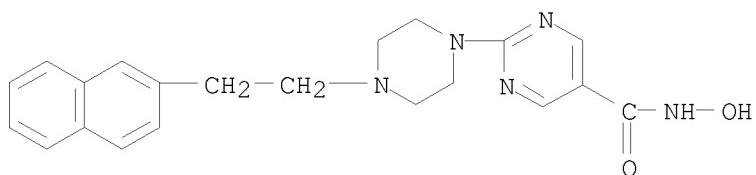
RN 603985-88-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl- (CA INDEX NAME)



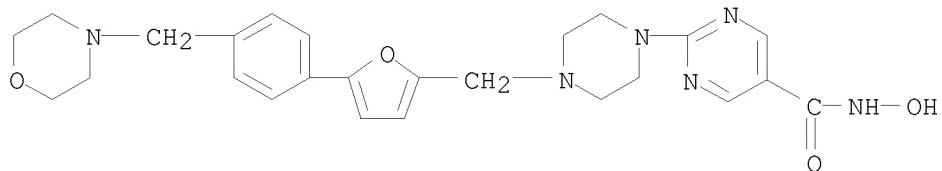
RN 603985-90-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl- (CA INDEX NAME)



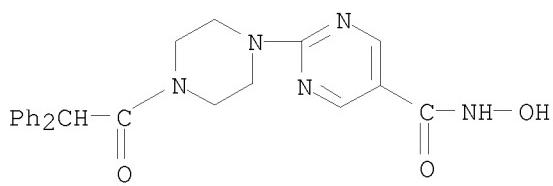
RN 603985-94-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl- (CA INDEX NAME)



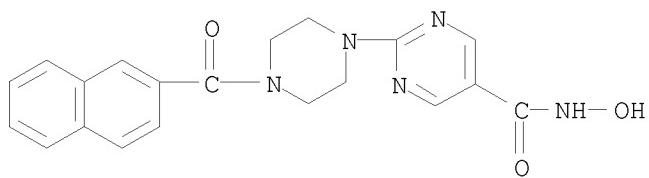
RN 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



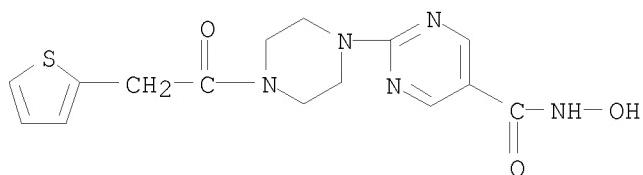
RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



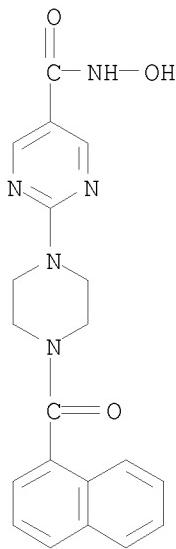
RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)

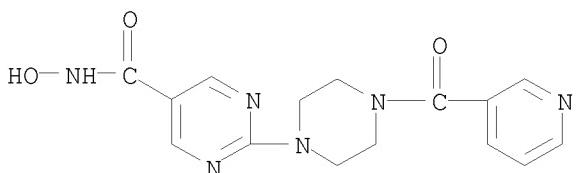


RN 603992-25-2 CAPLUS

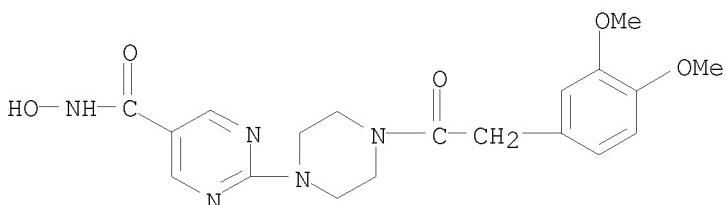
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



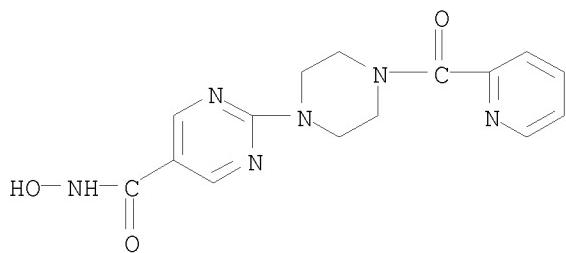
RN 603992-26-3 CAPLUS
 CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



RN 603992-27-4 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

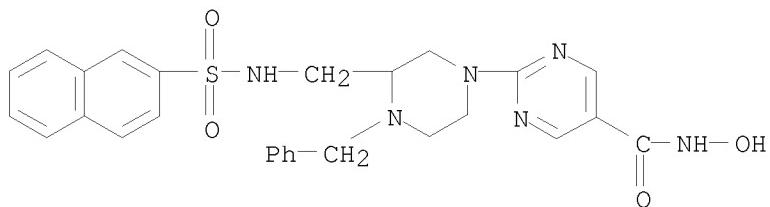


RN 603992-28-5 CAPLUS
 CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



RN 604784-81-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[3-[(2-naphthalenylsulfonyl)amino]methy]-4-(phenylmethyl)-1-piperazinyl- (CA INDEX NAME)



REFERENCE COUNT:

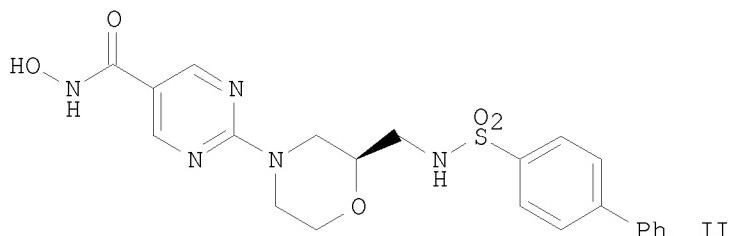
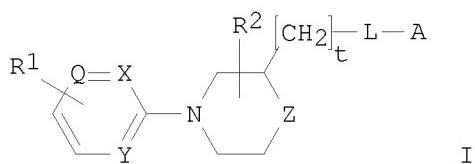
6

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN
 ACCESSION NUMBER: 2003:737757 CAPLUS
 DOCUMENT NUMBER: 139:276911
 TITLE: Preparation of N-(piperazinylmethyl-,
 piperidinylmethyl- and morpholinylmethyl) sulfonamides
 and amides as novel inhibitors of histone deacetylase
 INVENTOR(S): Van Emelen, Kristof
 PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.
 SOURCE: PCT Int. Appl., 69 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 8
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|------------------|-------------|
| WO 2003076438 | A1 | 20030918 | WO 2003-EP2510 | 20030311 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2475766 | A1 | 20030918 | CA 2003-2475766 | 20030311 |
| AU 2003218735 | A1 | 20030922 | AU 2003-218735 | 20030311 |
| EP 1485378 | A1 | 20041215 | EP 2003-711979 | 20030311 |
| EP 1485378 | B1 | 20080618 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| BR 2003007606 | A | 20041221 | BR 2003-7606 | 20030311 |
| CN 1642948 | A | 20050720 | CN 2003-805921 | 20030311 |
| JP 2005526766 | T | 20050908 | JP 2003-574655 | 20030311 |
| NZ 534833 | A | 20060728 | NZ 2003-534833 | 20030311 |
| CN 101007803 | A | 20070801 | CN 2007-10005212 | 20030311 |
| AT 398615 | T | 20080715 | AT 2003-711979 | 20030311 |
| TW 283676 | B | 20070711 | TW 2003-92105285 | 20030312 |
| IN 2004DN02536 | A | 20070413 | IN 2004-DN2536 | 20040831 |
| US 20050165016 | A1 | 20050728 | US 2004-507084 | 20040908 |
| MX 2004PA08795 | A | 20041126 | MX 2004-PA8795 | 20040910 |
| NO 2004004135 | A | 20040929 | NO 2004-4135 | 20040929 |
| PRIORITY APPLN. INFO.: | | | US 2002-363799P | P 20020313 |
| | | | WO 2002-EP14833 | A 20021223 |
| | | | CN 2003-805921 | A3 20030311 |
| | | | WO 2003-EP2510 | W 20030311 |

OTHER SOURCE(S): MARPAT 139:276911
 GI



AB The title compds. [I; t = 0-4; Q, X, Y = N, C; Z = NH, O, CH₂; R₁ = CONR₃R₄, NHCOR₇, CO(alkanediyl)SR₇, etc. (wherein R₃, R₄ = H, OH, alkyl, etc.; R₇ = H, alkyl, alkylcarbonyl, etc.); R₂ = H, OH, NH₂, etc.; L = NR₉CO, NR₉SO₂, NR₉CH₂ (R₉ = H, alkyl, cycloalkyl, etc.); A = (un)substituted Ph, cycloalkyl, pyridyl, etc.], having histone deacetylase inhibiting enzymic activity, were prepared and formulated. E.g., a multi-step synthesis of (+)-II which showed pIC₅₀ of 7.723 against HDAC, was given.

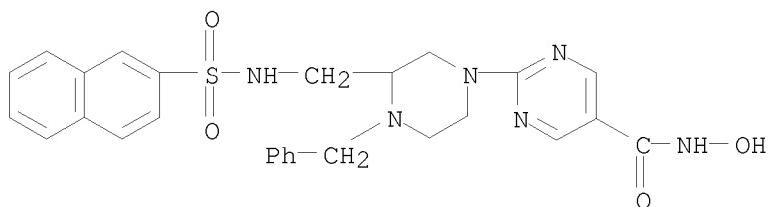
IT 604784-81-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of N-(piperazinylmethyl-, piperidinylmethyl- and morpholinylmethyl) sulfonamides and amides as novel inhibitors of histone deacetylase)

RN 604784-81-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[3-[(2-naphthalenylsulfonyl)amino]methoxy]-4-(phenylmethyl)-1-piperazinyl- (CA INDEX NAME)



REFERENCE COUNT:

2

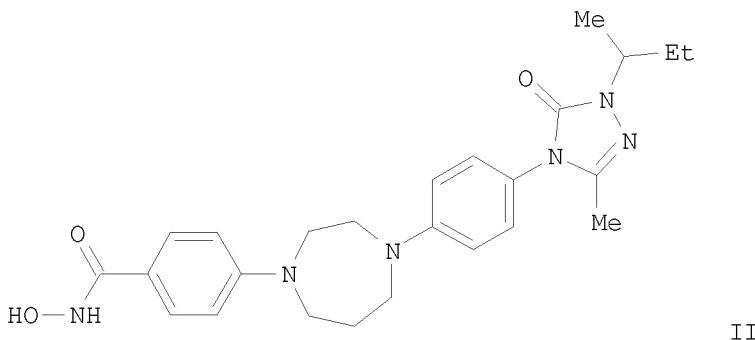
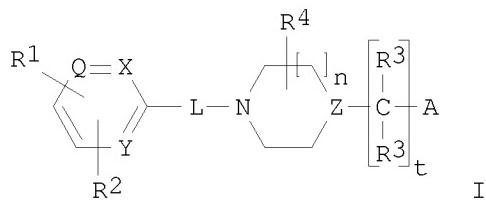
THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN
 ACCESSION NUMBER: 2003:737723 CAPLUS
 DOCUMENT NUMBER: 139:261309
 TITLE: Preparation of N-hydroxy-5-piperazino(piperidino or diazepino)-2-pyrimidinecarboxamides and N-hydroxy-4-piperazino(piperidino or diazepino)benzamides as new inhibitors of histone deacetylase
 INVENTOR(S): Angibaud, Patrick Rene; Pilatte, Isabelle Noeelle Constance; Van Brandt, Sven Franciscus Anna; Roux, Bruno; Ten Holte, Peter; Verdonck, Marc Gustaaf Celine; Meerpoel, Lieven; Dyatkin, Alexey Borisovich Janssen Pharmaceutica N.V., Belg.
 PATENT ASSIGNEE(S):
 SOURCE: PCT Int. Appl., 72 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 8
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|-------------|
| WO 2003076400 | A1 | 20030918 | WO 2003-EP2514 | 20030311 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2475764 | A1 | 20030918 | CA 2003-2475764 | 20030311 |
| AU 2003218736 | A1 | 20030922 | AU 2003-218736 | 20030311 |
| EP 1485353 | A1 | 20041215 | EP 2003-711980 | 20030311 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| BR 2003008081 | A | 20041221 | BR 2003-8081 | 20030311 |
| CN 1639125 | A | 20050713 | CN 2003-805675 | 20030311 |
| CN 1642551 | A | 20050720 | CN 2003-805833 | 20030311 |
| NZ 534834 | A | 20050729 | NZ 2003-534834 | 20030311 |
| JP 2005526067 | T | 20050902 | JP 2003-574621 | 20030311 |
| CN 101007803 | A | 20070801 | CN 2007-10005212 | 20030311 |
| IN 2004DN02533 | A | 20070413 | IN 2004-DN2533 | 20040831 |
| US 20050107384 | A1 | 20050519 | US 2004-506998 | 20040908 |
| ZA 2004007237 | A | 20050928 | ZA 2004-7237 | 20040909 |
| ZA 2004007235 | A | 20051004 | ZA 2004-7235 | 20040909 |
| ZA 2004007232 | A | 20051006 | ZA 2004-7232 | 20040909 |
| ZA 2004007233 | A | 20051006 | ZA 2004-7233 | 20040909 |
| ZA 2004007234 | A | 20051006 | ZA 2004-7234 | 20040909 |
| ZA 2004007236 | A | 20051006 | ZA 2004-7236 | 20040909 |
| MX 2004PA08806 | A | 20041126 | MX 2004-PA8806 | 20040910 |
| NO 2004004194 | A | 20041001 | NO 2004-4194 | 20041001 |
| PRIORITY APPLN. INFO.: | | | US 2002-363799P | P 20020313 |
| | | | WO 2002-EP14833 | A 20021223 |
| | | | CN 2003-805921 | A3 20030311 |

OTHER SOURCE(S):
GI

MARPAT 139:261309



AB The title compds. [I; n = 0-3; t = 0-4; Q, X, Y = N, C; Z = N, CH; R1 = CONR7R8, NHCOR9, CO(alkanediyl)SR9, etc. (wherein R7, R8 = H, OH, alkyl, etc.; R9 = H, alkyl, alkylcarbonyl, etc.); R2 = H, halo, OH, etc.; L = a bond, alkanediyl, alkanediyoxy, NH, CO, NHCO; each R3 = H and one H atom can be replaced by aryl; R4 = H, OH, NH2, etc.; A = (un)substituted Ph, cyclohexyl, pyridyl, etc.], having histone deacetylase inhibiting enzymic activity, were prepared and formulated. E.g., a multi-step synthesis of II which showed pIC50 of 5.121 against HDAC, was given.

IT 603985-87-1P 603985-89-3P 603985-91-7P
603985-95-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of piperazino(piperidino or diazepino) substituted 2-pyrimidinecarbohydroxamic acids and N-hydroxybenzamides as new inhibitors of histone deacetylase)

RN 603985-87-1 CAPLUS

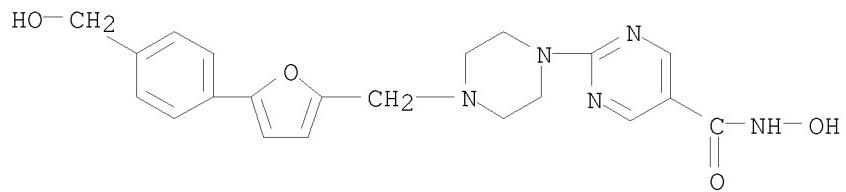
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-86-0

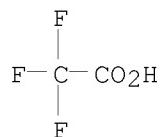
CMF C21 H23 N5 O4

10/513699



CM 2

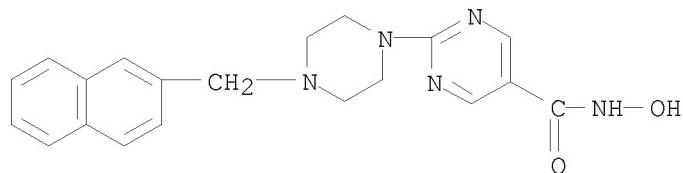
CRN 76-05-1
CMF C2 H F3 O2



RN 603985-89-3 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

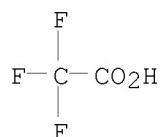
CM 1

CRN 603985-88-2
CMF C20 H21 N5 O2



CM 2

CRN 76-05-1
CMF C2 H F3 O2



RN 603985-91-7 CAPLUS

<12/04/2007>

Erich Leese

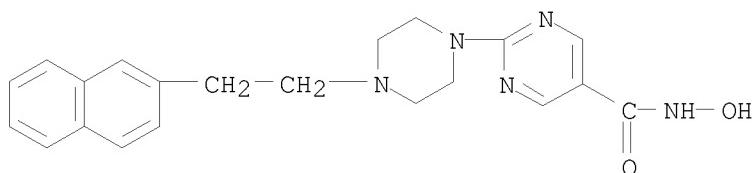
10/513699

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-90-6

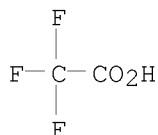
CMF C21 H23 N5 O2



CM 2

CRN 76-05-1

CMF C2 H F3 O2



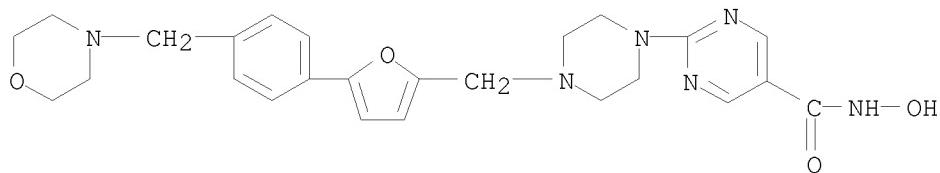
RN 603985-95-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl-, 2,2,2-trifluoroacetate (1:2) (CA INDEX NAME)

CM 1

CRN 603985-94-0

CMF C25 H30 N6 O4

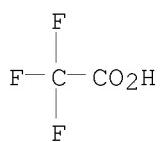


CM 2

CRN 76-05-1

CMF C2 H F3 O2

10/513699



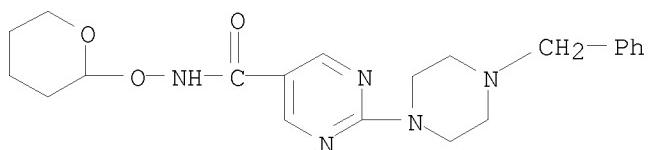
IT 603986-73-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of piperazino(piperidino or diazepino) substituted 2-pyrimidinecarbohydroxamic acids and N-hydroxybenzamides as new inhibitors of histone deacetylase)

RN 603986-73-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(phenylmethyl)-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)



REFERENCE COUNT:

3

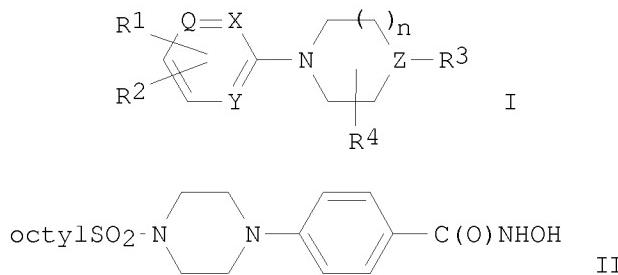
THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN
 ACCESSION NUMBER: 2003:737586 CAPLUS
 DOCUMENT NUMBER: 139:261308
 TITLE: Preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases
 INVENTOR(S): Van Emelen, Kristof; Verdonck, Marc Gustaaf Celine; Van Brandt, Sven Franciscus Anna; Angibaud, Patrick Rene; Meerpoel, Lieven; Dyatkin, Alexey Borisovich Janssen Pharmaceutica N.V., Belg.
 PATENT ASSIGNEE(S):
 SOURCE: PCT Int. Appl., 52 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 8
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|-------------|
| WO 2003075929 | A1 | 20030918 | WO 2003-EP2515 | 20030311 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2476065 | A1 | 20030918 | CA 2003-2476065 | 20030311 |
| AU 2003218737 | A1 | 20030922 | AU 2003-218737 | 20030311 |
| AU 2003218737 | B2 | 20080410 | | |
| EP 1485099 | A1 | 20041215 | EP 2003-711981 | 20030311 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| BR 2003007624 | A | 20050111 | BR 2003-7624 | 20030311 |
| CN 1639125 | A | 20050713 | CN 2003-805675 | 20030311 |
| CN 1642551 | A | 20050720 | CN 2003-805833 | 20030311 |
| JP 2005525379 | T | 20050825 | JP 2003-574203 | 20030311 |
| NZ 534832 | A | 20050930 | NZ 2003-534832 | 20030311 |
| CN 101007803 | A | 20070801 | CN 2007-10005212 | 20030311 |
| IN 2004DN02537 | A | 20070112 | IN 2004-DN2537 | 20040831 |
| ZA 2004007237 | A | 20050928 | ZA 2004-7237 | 20040909 |
| ZA 2004007235 | A | 20051004 | ZA 2004-7235 | 20040909 |
| ZA 2004007232 | A | 20051006 | ZA 2004-7232 | 20040909 |
| ZA 2004007233 | A | 20051006 | ZA 2004-7233 | 20040909 |
| ZA 2004007234 | A | 20051006 | ZA 2004-7234 | 20040909 |
| ZA 2004007236 | A | 20051006 | ZA 2004-7236 | 20040909 |
| MX 2004PA08797 | A | 20041126 | MX 2004-PA8797 | 20040910 |
| US 20050096468 | A1 | 20050505 | US 2004-507785 | 20040913 |
| NO 2004004113 | A | 20040928 | NO 2004-4113 | 20040928 |
| PRIORITY APPLN. INFO.: | | | US 2002-363799P | P 20020313 |
| | | | WO 2002-EP14833 | A 20021223 |
| | | | CN 2003-805921 | A3 20030311 |
| | | | WO 2003-EP2515 | W 20030311 |

OTHER SOURCE(S): MARPAT 139:261308

GI



AB This invention comprises aryl and heteroaryl hydroxamic acids (shown as I; variables defined below; e.g. II) having histone deacetylase inhibiting enzymic activity; their preparation, compns. containing them and their use as a medicine. Compds. I show excellent in-vitro histone deacetylase inhibiting enzymic activity, have advantageous properties with regard to cellular activity and specific properties with regard to inhibition of cell cycle progression at both G1 and G2 checkpoints (p21 induction capacity), and show good metabolic stability and high bioavailability and more particular show oral bioavailability. They can also be used for detection and identification of histone deacetylase. General synthetic procedures and characterization data for twenty-seven I are included; also, preps. of 12 intermediates are included. For example, a 59 % yield of 2-[4-(dimethylaminosulfonyl)piperazin-1-yl]pyrimidine-5-carbohydroxamic acid was obtained by removing the O-tetrahydropyranyl group of its ester using trifluoroacetic acid; the ester was prepared in 61 % yield from N'-(ethylcarbonimidoyl)-N,N-dimethyl-1,3-propanediamine monohydrochloride, sodium 2-[4-(dimethylaminosulfonyl)piperazin-1-yl]pyrimidine-5-carboxylate, O-(tetrahydro-2H-pyran-2-yl)hydroxylamine, and 1-hydroxy-1H-benzotriazole in CH₂Cl₂/THF. The sodium salt was obtained by base hydrolysis of the Et ester; the ester was prepared in 73 % yield from Et 2-(piperazin-1-yl)pyrimidine-5-carboxylate and dimethylsulfamoyl chloride; Et 2-(piperazin-1-yl)pyrimidine-5-carboxylate was obtained in <96 % yield from Et 2-(4-benzylpiperazin-1-yl)pyrimidine-5-carboxylate by hydrogenation using Pd/C; the benzyl derivative was obtained from 1-(phenylmethyl)piperazine, (135 mL) was added gradually to a solution of potassium carbonate (0.18 mol) and 2-(methylsulfonyl)-5-pyrimidinecarboxylic acid Et ester, K₂CO₃ in MeCN. For I: n is 0-3; Q, X and Y are N or C; Z is N or CH; R1 is -C(O)NR5R6, -N(H)C(O)R7, -C(O)-C1-6alkanediylSR7, -NR8C(O)N(OH)R7, -NR8C(O)C1-6alkanediylSR7, -NR8C(O)C:N(OH)R7 or another Zn-chelating-group; R2 is H, halo, hydroxy, amino, nitro, C1-6alkyl, C1-6alkyloxy, trifluoromethyl, di(C1-6-alkyl)amino, hydroxyamino or naphthalenylsulfonylpnazinyl. R3 is H, C1-6-alkyl, arylC2-6alkenediyl, furanylcarbonyl, naphthalenylcarbonyl, -C(O)phenylR9, C1-6alkylaminocarbonyl, aminosulfonyl, arylaminosulfonyl, aminosulfonylamino, di(C1-6-alkyl)aminosulfonylamino, arylaminosulfonylamino, aminosulfonylaminoc1-6-alkyl, di(C1-6-alkyl)aminosulfonylaminoc1-6-alkyl, arylaminosulfonylaminoc1-6alkyl, di(C1-6-alkyl)aminoC1-6alkyl, C11-12-alkylsulfonyl, di(C1-6-alkyl)aminosulfonyl, trihaloC1-6-alkylsulfonyl, di(aryl)C1-6alkylcarbonyl, thiophenylC1-6alkylcarbonyl, pyridinylcarbonyl or arylC1-6alkylcarbonyl. R4 is H, hydroxy, amino, hydroxyC1-6alkyl, C1-6alkyl, C1-6alkyloxy,

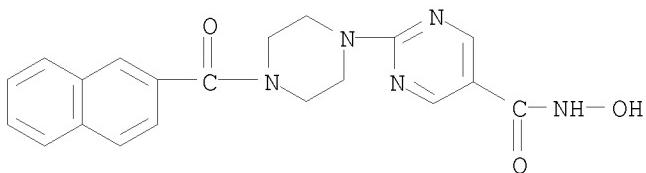
arylC1-6alkyl, aminocarbonyl, hydroxycarbonyl, aminoC1-6-alkyl, aminocarbonylC1-6-alkyl, hydroxycarbonylC1-6-alkyl, hydroxyaminocarbonyl, C1-6-alkyloxycarbonyl, C1-6-alkylaminoC1-6-alkyl or di(C1-6-alkyl)aminoC1-6-alkyl; when R3 and R4 are present on the same C atom, R3 and R4 together may form -C(O)-NH-CH₂-NR10- wherein R10 is H or aryl; when R3 and R4 are present on adjacent C atoms, R3 and R4 together may form :CH-CH:CH-CH: ; addnl. details are given in the claims.

IT 603991-96-4P
 RL: ARG (Analytical reagent use); PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate and reagent for detection/identification of histone deacetylase; preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases)

RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



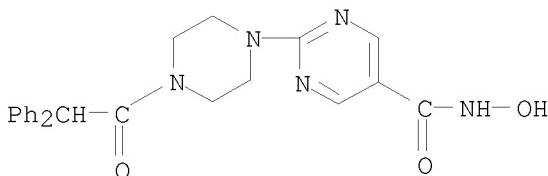
IT 603991-95-3P 603992-24-1P 603992-25-2P
 603992-26-3P 603992-27-4P 603992-28-5P

RL: ARG (Analytical reagent use); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate and reagent for detection/identification of histone deacetylase; preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases)

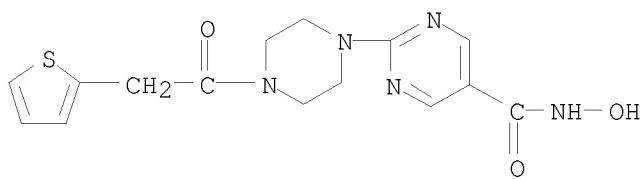
RN 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



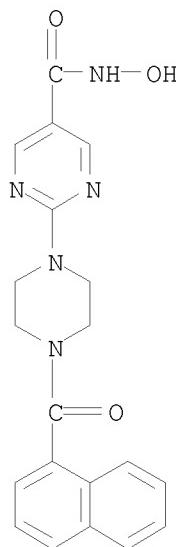
RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)



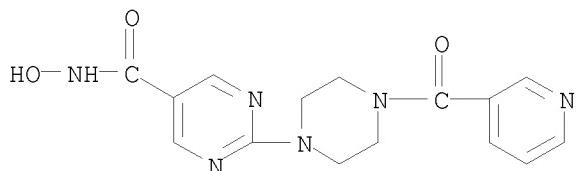
RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



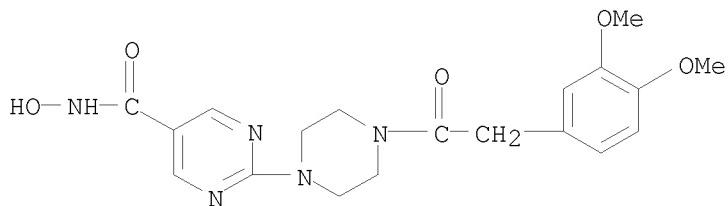
RN 603992-26-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



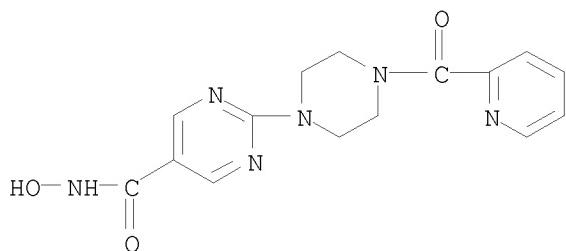
RN 603992-27-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

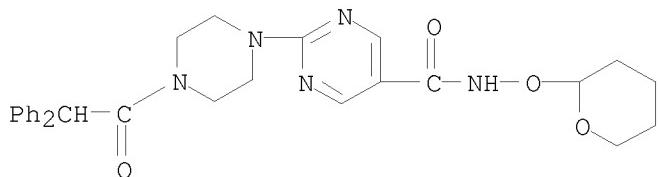


IT 603992-32-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases)

RN 603992-32-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)



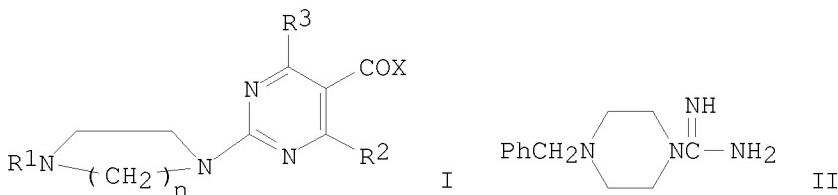
REFERENCE COUNT:

6

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN
 ACCESSION NUMBER: 1986:442843 CAPLUS
 DOCUMENT NUMBER: 105:42843
 ORIGINAL REFERENCE NO.: 105:7101a, 7104a
 TITLE: Pyrimidinylpiperazines
 INVENTOR(S): Kihara, Noriaki; Ishida, Tatsukazu; Isayama, Shigeru;
 Ishitoku, Takeshi; Tan, Hiroaki; Takahashi, Katsuya
 PATENT ASSIGNEE(S): Mitsui Petrochemical Industries, Ltd., Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 28 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|----------|
| JP 61043173 | A | 19860301 | JP 1984-163771 | 19840806 |
| JP 05022702 | B | 19930330 | | |
| PRIORITY APPLN. INFO.: | | | JP 1984-163771 | 19840806 |
| GI | | | | |

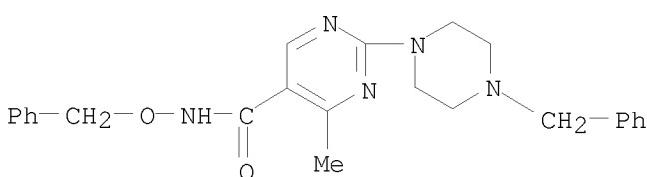


AB The title compds. [I, R1 = H, substituted Me, alkoxy carbonyl; R2, R3 = H, substituted alkyl; X = alkoxy, OH, (substituted) NH2; n = 2, 3], useful as herbicides against common weeds (no data), were prepared. Thus, the piperazinecarboxamidine derivative II sulfate reacted with MeOCH:C(COMe)CO2Me in MeOH/aqueous NaOH at room temperature overnight to give 88% I (R1 = PhCH2, n = 2, R2 = H, R3 = Me, X = OMe).

IT 102976-25-0P 102976-32-9P
 RL: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of, as herbicide)

RN 102976-25-0 CAPLUS

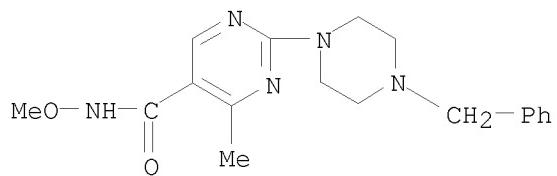
CN 5-Pyrimidinecarboxamide, 4-methyl-N-(phenylmethoxy)-2-[4-(phenylmethyl)-1-piperazinyl]- (CA INDEX NAME)



10/513699

RN 102976-32-9 CAPLUS

CN 5-Pyrimidinecarboxamide, N-methoxy-4-methyl-2-[4-(phenylmethyl)-1-piperazinyl]- (CA INDEX NAME)



10/513699

| => file reg | SINCE FILE ENTRY | TOTAL SESSION |
|--|------------------|---------------|
| COST IN U.S. DOLLARS | 60.43 | 239.00 |
| FULL ESTIMATED COST | | |
| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
| CA SUBSCRIBER PRICE | -8.80 | -8.80 |

FILE 'REGISTRY' ENTERED AT 16:02:33 ON 15 SEP 2008
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2008 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 14 SEP 2008 HIGHEST RN 1049627-95-3
DICTIONARY FILE UPDATES: 14 SEP 2008 HIGHEST RN 1049627-95-3

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH July 5, 2008.

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/support/stngen/stndoc/properties.html>

=>
Uploading C:\Program Files\Stnexp\Queries\10506998jason.str



chain nodes :
 1 2 4 11
 ring nodes :
 5 6 7 8 9 10
 chain bonds :
 1-4 5-11
 ring bonds :
 5-6 5-7 6-8 7-9 8-10 9-10
 exact/norm bonds :
 1-4 5-6 5-7 5-11 6-8 7-9 8-10 9-10

G1:C,N

Match level :
 1:Atom 2:Atom 4:CLASS 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:CLASS
 Generic attributes :
 1:
 Saturation : Unsaturated
 Number of Carbon Atoms : less than 7
 Type of Ring System : Monocyclic

 Element Count :
 Node 1: Limited
 C,C3-6
 N,N0-3

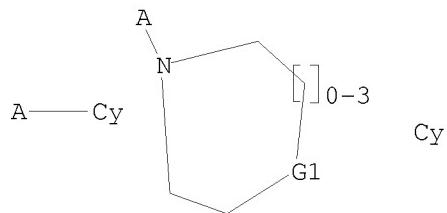
10/513699

L4 STRUCTURE UPLOADED

=> d 14

L4 HAS NO ANSWERS

L4 STR

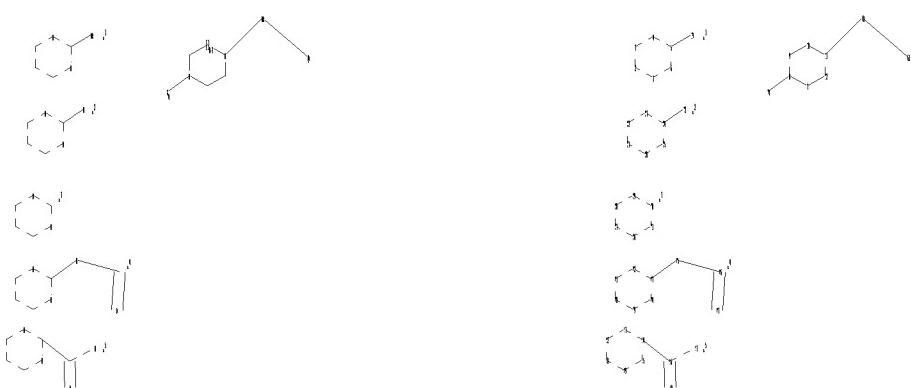


G1 C,N

Structure attributes must be viewed using STN Express query preparation.

=>

Uploading C:\Program Files\Stnexp\Queries\10506998election.str



chain nodes :

19 32 34 45 46 47 56 57 58 60 61

ring nodes :

1 2 3 4 5 6 7 8 9 10 11 12 20 21 22 23 24 25 26 27 28 29 30
31 39 40 41 42 43 44 49 50 52 53 54 55

chain bonds :

<12/04/2007>

Erich Leese

10/513699

5-19 8-34 11-60 24-32 43-45 45-46 46-47 54-56 56-57 56-58 60-61
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12 20-21 20-25
21-22 22-23 23-24 24-25 26-27 26-31 27-28 28-29 29-30 30-31 39-40 39-44
40-41 41-42 42-43 43-44 49-50 49-55 50-52 52-53 53-54 54-55
exact/norm bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-19 7-8 7-12 8-9 8-34 9-10 10-11 11-12 11-60
20-21 20-25 21-22 22-23 23-24 24-25 24-32 26-27 26-31 27-28 28-29 29-30
30-31 39-40 39-44 40-41 41-42 42-43 43-44 43-45 45-46 46-47 49-50 49-55
50-52 52-53 53-54 54-55 56-57 56-58 60-61

exact bonds :

54-56

isolated ring systems :

containing 1 : 7 : 20 : 26 : 39 : 49 :

G1:C,N

G2:Ak,NH2,NO2

G3:O

G4:[*1], [*2], [*3], [*4], [*5]

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 19:CLASS 20:Atom 21:Atom 22:Atom 23:Atom 24:Atom 25:Atom
26:Atom 27:Atom 28:Atom 29:Atom 30:Atom 31:Atom 32:CLASS 34:CLASS 39:Atom
40:Atom 41:Atom 42:Atom 43:Atom 44:Atom 45:CLASS 46:CLASS 47:CLASS 49:Atom
50:Atom 52:Atom 53:Atom 54:Atom 55:Atom 56:CLASS 57:CLASS 58:CLASS 60:CLASS
61:Atom

L5 STRUCTURE UPLOADED

=> d 15

L5 HAS NO ANSWERS

L5 STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.

=> s 15 full

FULL SEARCH INITIATED 16:04:21 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 596714 TO ITERATE

100.0% PROCESSED 596714 ITERATIONS
SEARCH TIME: 00.00.08

10223 ANSWERS

L6 10223 SEA SSS FUL L5

=> file caplus

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

10/513699

| | ENTRY | SESSION |
|--|------------|---------|
| FULL ESTIMATED COST | 179.28 | 418.28 |
| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE | TOTAL |
| CA SUBSCRIBER PRICE | ENTRY | SESSION |
| | 0.00 | -8.80 |

FILE 'CAPLUS' ENTERED AT 16:04:37 ON 15 SEP 2008
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2008 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 15 Sep 2008 VOL 149 ISS 12
FILE LAST UPDATED: 14 Sep 2008 (20080914/ED)

Caplus now includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2008.

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

<http://www.cas.org/legal/infopolicy.html>

=> s 16 full
L7 4042 L6

=> s 17 and py<2003
22958911 PY<2003
L8 2880 L7 AND PY<2003

| | SINCE FILE | TOTAL |
|--|------------|---------|
| COST IN U.S. DOLLARS | ENTRY | SESSION |
| FULL ESTIMATED COST | 3.56 | 421.84 |
| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE | TOTAL |
| CA SUBSCRIBER PRICE | ENTRY | SESSION |
| | 0.00 | -8.80 |

FILE 'REGISTRY' ENTERED AT 16:06:14 ON 15 SEP 2008
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2008 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

10/513699

STRUCTURE FILE UPDATES: 14 SEP 2008 HIGHEST RN 1049627-95-3
DICTIONARY FILE UPDATES: 14 SEP 2008 HIGHEST RN 1049627-95-3

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH July 5, 2008.

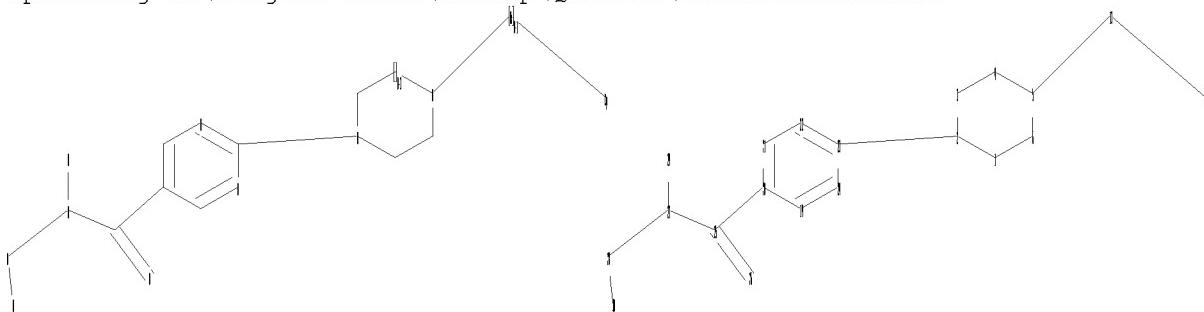
Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/support/stngen/stndoc/properties.html>

=>

Uploading C:\Program Files\Stnexp\Queries\10506998three.str



chain nodes :

13 14 25 26 27 28 29 30

ring nodes :

1 2 3 4 5 6 19 20 21 22 23 24

chain bonds :

2-23 5-13 13-14 20-25 25-26 25-27 27-28 27-29 28-30

ring bonds :

1-2 1-6 2-3 3-4 4-5 5-6 19-20 19-24 20-21 21-22 22-23 23-24

exact/norm bonds :

1-2 1-6 2-3 2-23 3-4 4-5 5-6 5-13 13-14 25-26 25-27 27-28

exact bonds :

20-25 27-29 28-30

normalized bonds :

19-20 19-24 20-21 21-22 22-23 23-24

isolated ring systems :

containing 1 :

G1:C,N

G2:Ak,NH2,NO2

G3:O

10/513699

G4

G5:C,N,Zn,H

Match level :

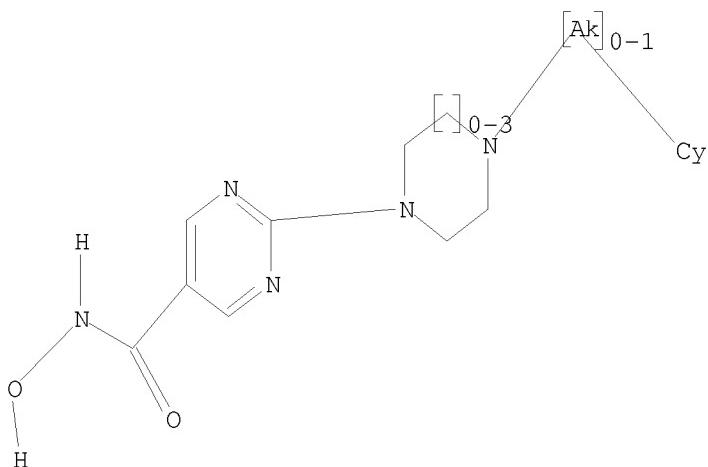
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 13:CLASS 14:Atom 19:Atom 20:Atom
21:Atom 22:Atom 23:Atom 24:Atom 25:CLASS 26:CLASS 27:CLASS 28:CLASS
29:CLASS 30:CLASS

L9 STRUCTURE UPLOADED

=> d 19

L9 HAS NO ANSWERS

L9 STR



G1 C,N

G2 Ak,NH2,NO2

G3 O

G4

G5 C,N,Zn,H

Structure attributes must be viewed using STN Express query preparation.

=> s 19 full

FULL SEARCH INITIATED 16:07:27 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 433 TO ITERATE

100.0% PROCESSED 433 ITERATIONS
SEARCH TIME: 00.00.01

112 ANSWERS

L10 112 SEA SSS FUL L9

=> file caplus

10/513699

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|--|------------------|---------------|
| FULL ESTIMATED COST | 178.82 | 600.66 |
| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
| CA SUBSCRIBER PRICE | 0.00 | -8.80 |

FILE 'CAPLUS' ENTERED AT 16:07:34 ON 15 SEP 2008
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2008 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 15 Sep 2008 VOL 149 ISS 12
FILE LAST UPDATED: 14 Sep 2008 (20080914/ED)

Caplus now includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2008.

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

<http://www.cas.org/legal/infopolicy.html>

=> s l10 full

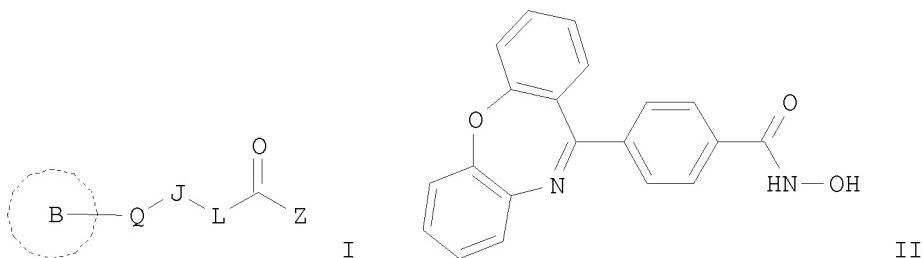
L11 13 L10

=> d ibib abs hitstr tot

L11 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2008:556979 CAPLUS
DOCUMENT NUMBER: 148:538314
TITLE: Preparation of tricyclic hydroxamic acids as
inhibitors of histone deacetylase
INVENTOR(S): Shapiro, Gideon; Moncuso, John; Pierre, Tessier; Leit,
Silvana; Deziel, Robert; David, Smil; Richard,
Chesworth; Chantigny, Yves Andre; Patrick, Beaulieu
PATENT ASSIGNEE(S): Methygene Inc., Can.; En Vivo Pharmaceuticals, Inc.
SOURCE: PCT Int. Appl., 405pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2008055068 | A2 | 20080508 | WO 2007-US82668 | 20071026 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG,
KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL,
PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW,
GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM | | | | |
| US 20080207590 | A1 | 20080828 | US 2007-925151 | 20071026 |
| PRIORITY APPLN. INFO.: | | | | |
| US 2006-863347P P 20061028 | | | | |
| US 2007-884287P P 20070110 | | | | |

OTHER SOURCE(S): MARPAT 148:538314
GI

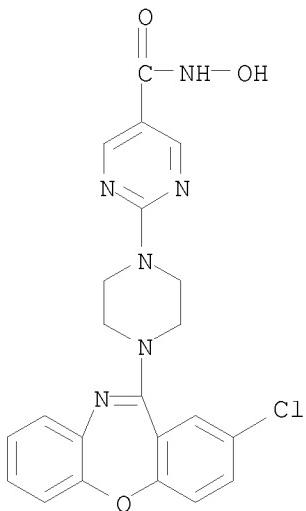


AB The title compds. I [Z = N(R1)OR2, H; L = a bond, N(OR2); when L = N(OR2), Z = H; when Z = H, L = N(OR2); R1, R2 = H, alkyl, aryl, etc.; J = a bond, :CH-, alkyl, alkyl(heteroalkyl)alkyl, etc.; Q = diazepine, pyrrolidine, diazabicyclo[3.3.1]nonane, etc.; B = dibenzo[b,f][1,4]oxazepine, benzo[b]pyrido[2,3-e][1,4]diazepine, benzo[f]thieno[2,3-b][1,4]oxazepine, etc.], useful for the inhibition of histone deacetylase, were prepared E.g., a 3-step synthesis of II, starting from 10,11-

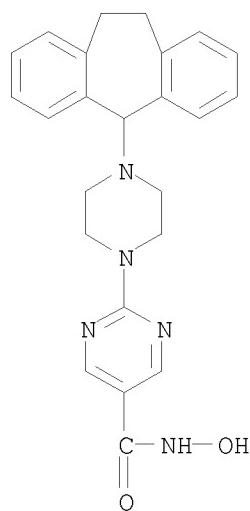
10/513699

dihydrodibenz[b,f][1,4]oxazepin-11-one, was given. All exemplified compds. I have an IC₅₀ of ≤ 10 μM against one or more of HDAC-1 through HDAC-11 (data for representative compds. I were given). Pharmaceutical composition comprising the compound I and methods of treating polyglutamine (polyQ) expansion diseases such as Huntington's disease, are disclosed.

IT 1024007-45-1P 1024009-50-4P 1024009-80-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of tricyclic hydroxamic acids as inhibitors of histone deacetylase)
RN 1024007-45-1 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-(2-chlorodibenz[b,f][1,4]oxazepin-11-yl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

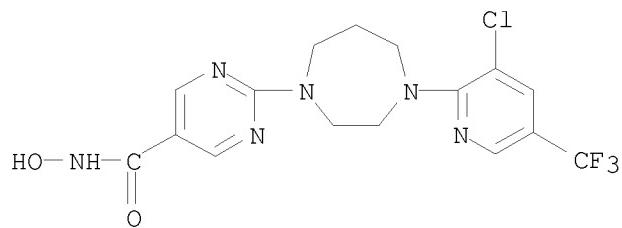


RN 1024009-50-4 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



RN 1024009-80-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]hexahydro-1H-1,4-diazepin-1-yl]-N-hydroxy- (CA INDEX NAME)

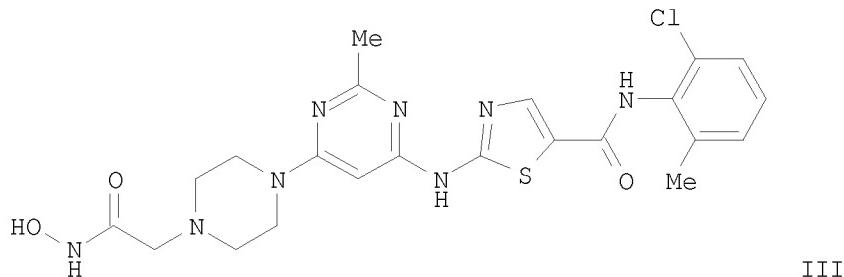
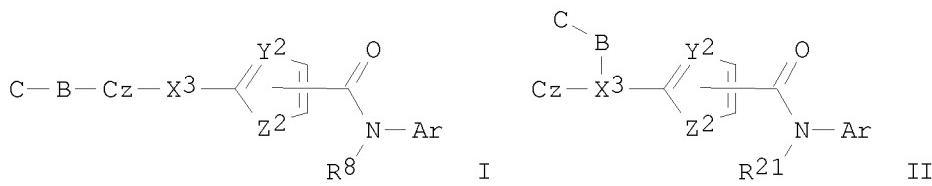


10/513699

L11 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2008:353109 CAPLUS
DOCUMENT NUMBER: 148:379651
TITLE: Pyrimidine derivatives as tyrosine kinase inhibitors containing a zinc binding moiety and their preparation
INVENTOR(S): Cai, Xiong; Qian, Changgeng; Gould, Stephen; Zhai, Haixiao
PATENT ASSIGNEE(S): Curis, Inc., USA
SOURCE: PCT Int. Appl., 81pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2008033746 | A2 | 20080320 | WO 2007-US77970 | 20070910 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| US 20080125440 | A1 | 20080529 | US 2007-852450 | 20070910 |
| PRIORITY APPLN. INFO.: | | | US 2006-843730P | P 20060911 |
| | | | US 2007-895901P | P 20070320 |

OTHER SOURCE(S): MARPAT 148:379651
GI



AB The invention relates to tyrosine kinase inhibitors of formula I and II that contain a zinc-binding moiety and their use in the treatment of tyrosine related diseases and disorders such as cancer. The said derivs. may further act as HDAC inhibitors. Compds. of formula I and II wherein Cz is (un)substituted (hetero)aryl, and (un)substituted heterocyclic; Ar is (un)substituted (hetero)aryl; X3 is NH, alkylamino, O, and S; Z2 is O, S, NH and alkylamino; Y2 is N, CH, C-halo, C-(hetero)aryl, etc.; R21 is H and aliphatic; B is a liner. C is urea, thiourea, acetyl, thioacetyl, etc.; R8 is H, acyl, and (un)substituted aliphatic group; and their geometric isomers, enantiomers, diastereoisomers, racemates, pharmaceutically acceptable salts, and solvates thereof, are claimed. Example compound III was prepared by a multistep procedure (procedure given). All the invention compds. were evaluated for their tyrosine kinase inhibitory activity.

IT 1012886-07-5P

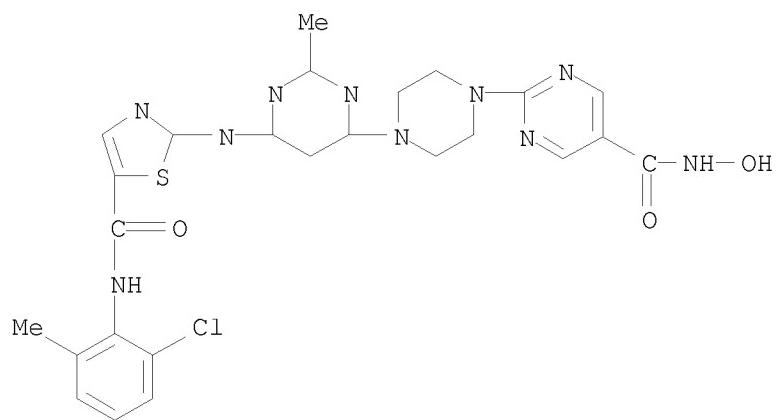
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrimidine derivs. as tyrosine kinase inhibitors containing a zinc binding moiety)

RN 1012886-07-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[6-[[5-[(2-chloro-6-methylphenyl)amino]carbonyl]-2-thiazolyl]amino]-2-methyl-4-pyrimidinyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

10/513699



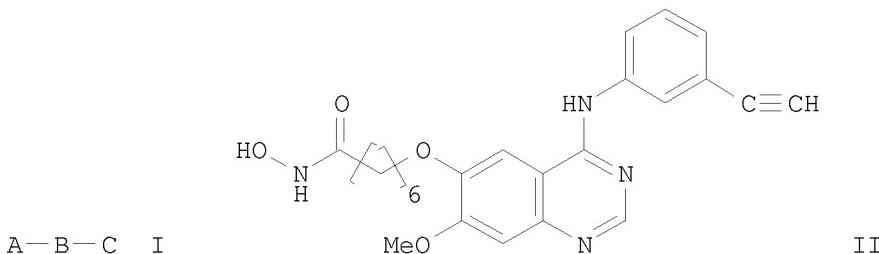
ONE OR MORE TAUTOMERIC DOUBLE BONDS NOT DISPLAYED IN THE STRUCTURE

L11 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN
 ACCESSION NUMBER: 2008:353001 CAPLUS
 DOCUMENT NUMBER: 148:355828
 TITLE: Multi-functional small molecules as anti-proliferative agents and their preparation
 INVENTOR(S): Cai, Xiong; Qian, Changgeng; Gould, Stephen; Zhai, Haixiao
 PATENT ASSIGNEE(S): Curis, Inc., USA
 SOURCE: PCT Int. Appl., 494pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2008033747 | A2 | 20080320 | WO 2007-US77971 | 20070910 |
| WO 2008033747 | A9 | 20080724 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA | | | | |
| US 20080221132 | A1 | 20080911 | US 2007-852458 | 20070910 |
| PRIORITY APPLN. INFO.: | | | US 2006-843590P | P 20060911 |
| | | | US 2007-895889P | P 20070320 |

OTHER SOURCE(S): MARPAT 148:355828

GI



AB The invention relates to the compns., methods, and applications of an approach to selective inhibition of several cellular or mol. targets with a single small mol. More specifically, the present invention relates to multi-functional small mols. of formula I wherein one functionality is capable of inhibiting histone deacetylases (HDAC) and the other

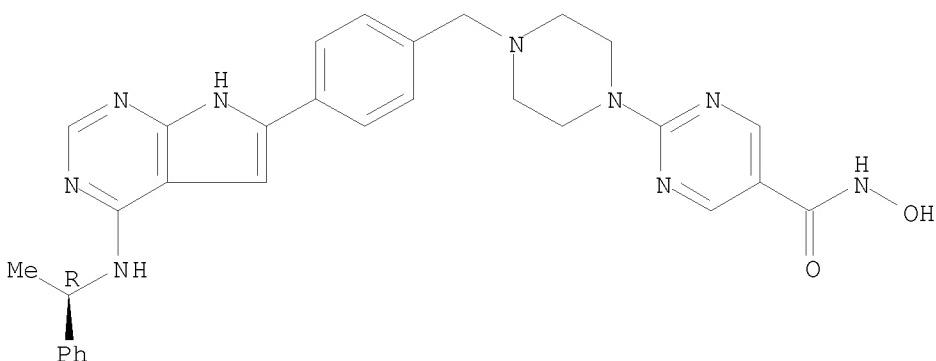
functionality is capable of inhibiting a different cellular or mol. pathway involved in aberrant cell proliferation, differentiation or survival. Compds. of formula I wherein A is a pharmacophore of an anticancer agent capable of inhibiting at least one cellular or mol. pathway involved in the aberrant cell proliferation, differentiation or survival; B is a linker; C is a zinc-binding moiety; and their geometrical isomers, enantiomers, diastereoisomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, are claimed. Example compound II was prepared by a multistep procedure (procedure given). All the invention compds. were evaluated for their antiproliferative activity (some data given).

IT 1011716-90-7P 1012886-07-5P
 RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRPH (Prophetic); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prophetic starting material; preparation of multi-functional small mols. as antiproliferative agents)

RN 1011716-90-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[4-[(1R)-1-phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methyl]-1-piperazinyl- (CA INDEX NAME)

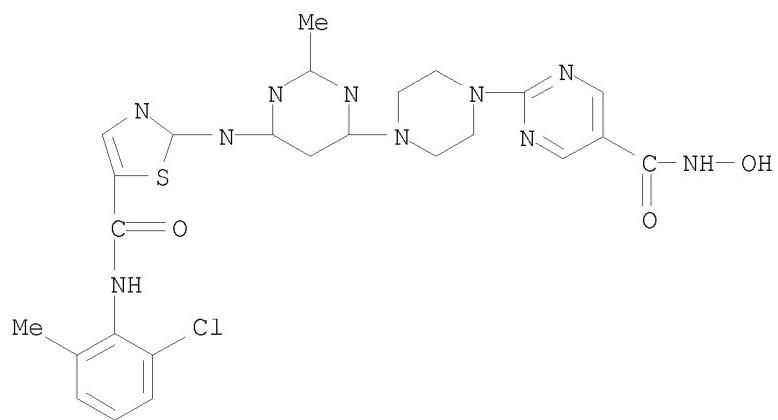
Absolute stereochemistry.



RN 1012886-07-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[6-[[5-[(2-chloro-6-methylphenyl)amino]carbonyl]-2-thiazoly]amino]-2-methyl-4-pyrimidinyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

10/513699



ONE OR MORE TAUTOMERIC DOUBLE BONDS NOT DISPLAYED IN THE STRUCTURE

L11 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN
 ACCESSION NUMBER: 2008:351928 CAPLUS
 DOCUMENT NUMBER: 148:355814
 TITLE: Preparation of (aralkylamino)(phenyl)pyrrolo[2,3-d]pyrimidine derivatives for use as protein tyrosine kinase (PTK) inhibitors
 INVENTOR(S): Cai, Xiong; Qian, Changgeng; Gould, Stephen
 PATENT ASSIGNEE(S): Curis, Inc., USA
 SOURCE: PCT Int. Appl., 123pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2008033745 | A2 | 20080320 | WO 2007-US77968 | 20070910 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| US 20080161320 | A1 | 20080703 | US 2007-852440 | 20070910 |
| PRIORITY APPLN. INFO.: | | | US 2006-843646P | P 20060911 |
| | | | US 2007-895894P | P 20070320 |

OTHER SOURCE(S): MARPAT 148:355814
 GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Fused bicyclic pyrimidine derivs. I and II [Ar = aryl, substituted arylheteroaryl or heteroaryl; Q = absent or (un)substituted alkyl; X = O, S, NH, or aralkylamino; Z = O, S, NR1; Y = N or CR2; B = linker; D = C(O)NH2, NHC(S)CH3, CHC(O)NHacyl, etc.; R1 = H or (un)substituted alkyl; R2 = H, halo, (un)substituted aliphatic, aryl or heteroaryl], and their pharmaceutically acceptable salts, are prepared and disclosed as protein tyrosine kinase (PTK) inhibitors. Thus, e.g., III was prepared by N-alkylation of 1,4-dioxa-8-azaspiro[4.5]decane with 6-(4-(chloromethyl)phenyl)-N-((R)-1-phenylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (preparation given) and deprotection followed by condensation with 6-aminohexanoic acid Me ester and amidation with hydroxylamine. Select I were evaluated in EGFR assays, e.g., III demonstrated an IC50 value of ≤ 0.1 (μ M).

IT 1011716-90-7P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

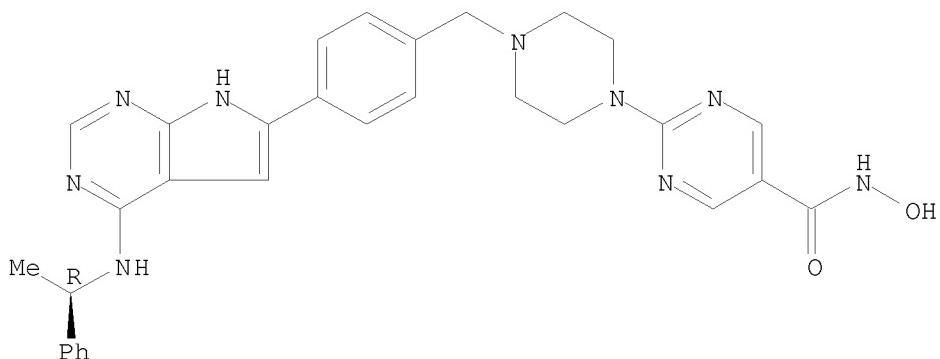
(Uses)

(preparation of (aralkylamino)(phenyl)pyrrolopyrimidine derivs. for use as protein tyrosine kinase (PTK) inhibitors)

RN 1011716-90-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[4-[[4-[(1R)-1-phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

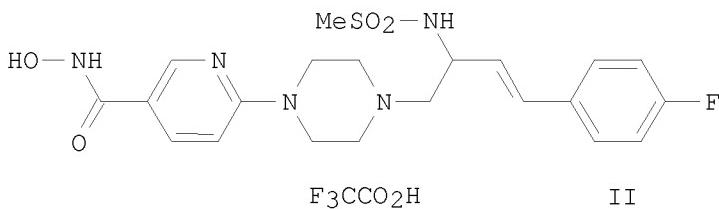
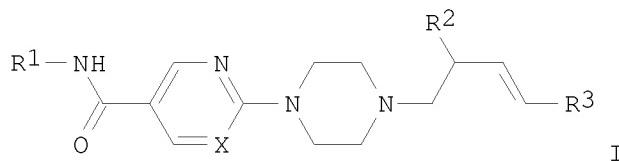
Absolute stereochemistry.



L11 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN
 ACCESSION NUMBER: 2007:816930 CAPLUS
 DOCUMENT NUMBER: 147:211903
 TITLE: Preparation of pyrimidine derivatives as histone deacetylase inhibitors
 INVENTOR(S): Marconnet-Decrane, Laurence Francoise Bernadette; Gaurrand, Sandrine Francoise Dominique; Angibaud, Patrick Rene
 PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.
 SOURCE: PCT Int. Appl., 62pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2007082874 | A1 | 20070726 | WO 2007-EP50371 | 20070116 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN,
KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK,
MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO,
RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT,
TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM | | | | |
| CA 2630717 | A1 | 20070726 | CA 2007-2630717 | 20070116 |
| PRIORITY APPLN. INFO.: | | | EP 2006-100570 | A 20060119 |
| | | | WO 2007-EP50371 | W 20070116 |

OTHER SOURCE(S): MARPAT 147:211903
 GI



AB The title compds. with general formula I [wherein R1 = OH or substituted phenyl; X = N or CH; R2 = amino, alkylamino, alkoxy, OH, etc.; R3 = (un)substituted Ph, naphthalene, or heterocycle] or N-oxide forms, pharmaceutically acceptable salts, or stereoisomeric forms thereof were prepared as histone deacetylase (HDAC) inhibitors for the treatment of proliferative diseases. For example, compound II was prepared in a multi-step synthesis. In vitro assay for inhibition of HDAC was performed to measure the inhibition of HDAC enzymic activity, and colorimetric assay was performed to determine cellular activity on A2780 tumor cells. II showed HDAC inhibitory and anti-proliferative activities in the above two assays with pIC₅₀ values of 7.0 and 5.3, resp. Formulations containing I as active ingredients were also reported.

IT 944738-91-4P 944738-94-7P 944738-97-0P

944739-00-8P 944739-08-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrimidine derivs. as histone deacetylase inhibitors)

RN 944738-91-4 CAPLUS

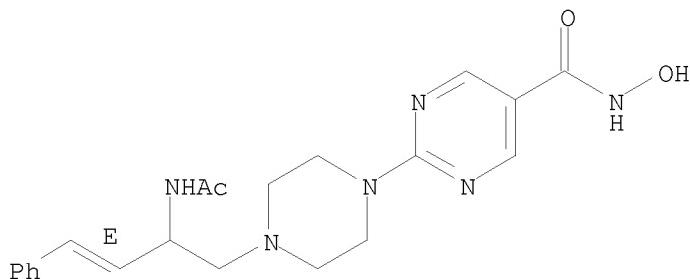
CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(acetylamino)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-90-3

CMF C21 H26 N6 O3

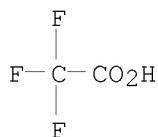
Double bond geometry as shown.



CM 2

CRN 76-05-1

CMF C2 H F3 O2



10/513699

RN 944738-94-7 CAPLUS

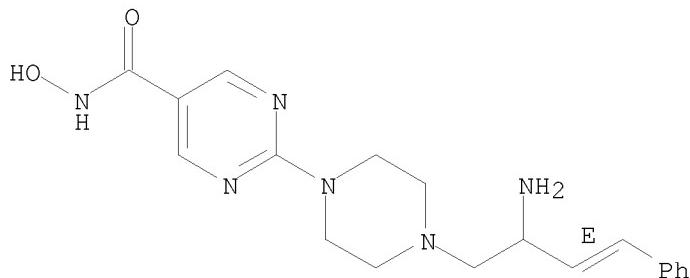
CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-amino-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-93-6

CMF C19 H24 N6 O2

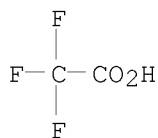
Double bond geometry as shown.



CM 2

CRN 76-05-1

CMF C2 H F3 O2



RN 944738-97-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(2,5-dioxo-1-pyrrolidinyl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

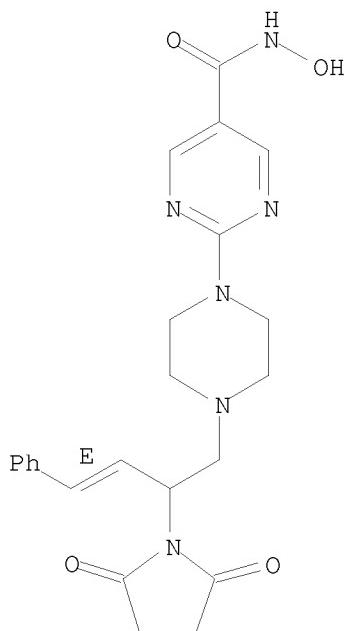
CM 1

CRN 944738-96-9

CMF C23 H26 N6 O4

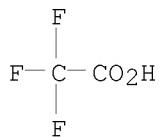
Double bond geometry as shown.

10/513699



CM 2

CRN 76-05-1
CMF C2 H F3 O2



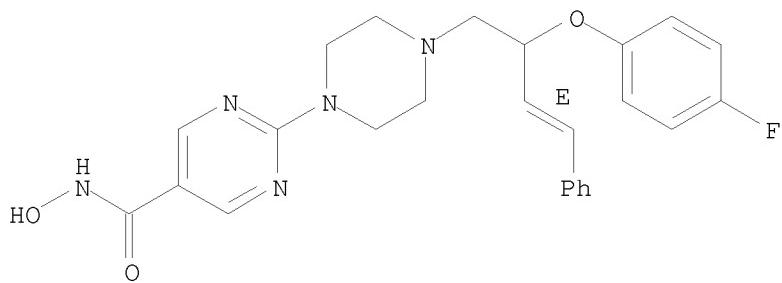
RN 944739-00-8 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(4-fluorophenoxy)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-99-2
CMF C25 H26 F N5 O3

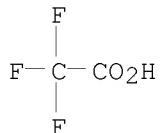
Double bond geometry as shown.

10/513699



CM 2

CRN 76-05-1
CMF C2 H F3 O2

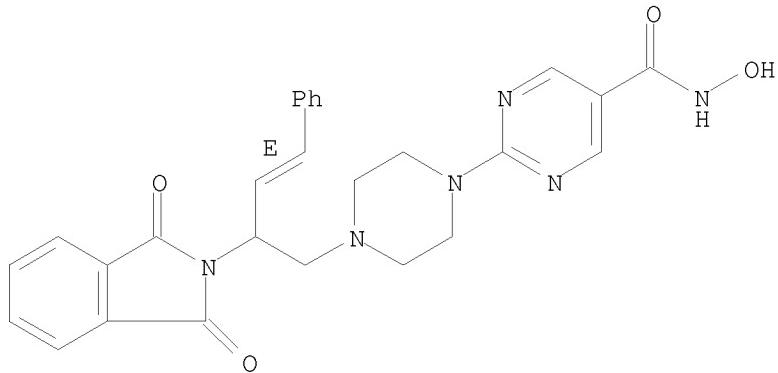


RN 944739-08-6 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944739-07-5
CMF C27 H26 N6 O4

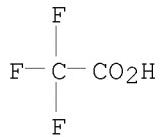
Double bond geometry as shown.



CM 2

10/513699

CRN 76-05-1
CMF C2 H F3 O2



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/513699

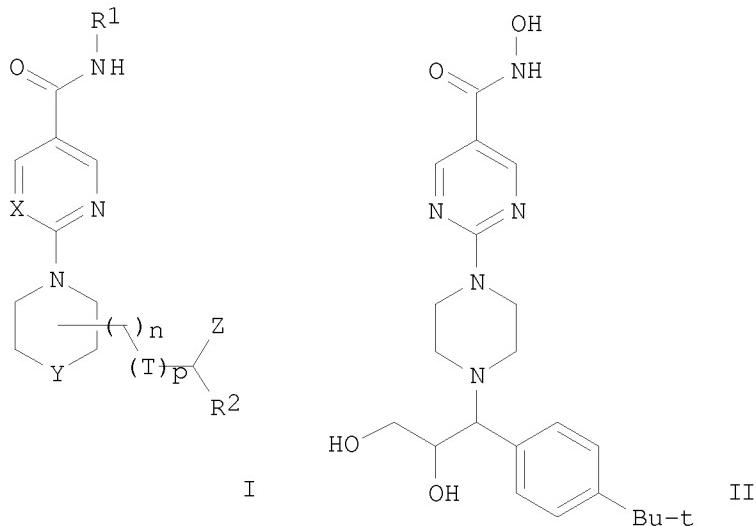
L11 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:816806 CAPLUS
DOCUMENT NUMBER: 147:211902
TITLE: Preparation of pyrimidine derivatives as histone deacetylase inhibitors
INVENTOR(S): Angibaud, Patrick Rene; Van Brandt, Sven Franciscus Anna; Marconnet-Decrane, Laurence Francoise Bernadette; Roux, Bruno
PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.
SOURCE: PCT Int. Appl., 63pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2007082880 | A1 | 20070726 | WO 2007-EP50379 | 20070116 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |

PRIORITY APPLN. INFO.: EP 2006-100571 A 20060119

OTHER SOURCE(S): MARPAT 147:211902

GI



AB The title compds. with general formula I [wherein R1 = OH or substituted phenyl; R2 = -CH₂OH, -CH₂OCH₃, -CH₂OCH₂CH₃, or -CH₂CH(OH)CH₂OH; T = N(R₃), where R₃ = H, alkyl, cycloalkyl, etc.; X = N or CH; Y = O, NH, CH₂, etc.; n = 0-1; p = 0-1, provided that when p = 0 then n = 0 and Y = N, and -CH(R₂)-Z is attached to Y; Z = (un)substituted aryl or heteroaryl] or N-oxide forms, pharmaceutically acceptable salts, or stereoisomeric forms thereof were prepared as histone deacetylase (HDAC) inhibitors for the treatment of proliferative diseases. For example, compound II was prepared in a multi-step synthesis. In vitro assay for inhibition of HDAC was performed to measure the inhibition of HDAC enzymic activity, and colorimetric assay was performed to determine cellular activity on A2780 tumor cells. II showed HDAC inhibitory and anti-proliferative activities in the above two assays with pIC₅₀ values of 7.0 and 7.1, resp. Formulations containing I as active ingredients were also reported.

IT 944712-03-2P 944712-05-4P 944712-07-6P
 944712-09-8P 944712-10-1P 944712-12-3P

944712-14-5P 944712-16-7P 944712-18-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrimidine derivs. as histone deacetylase inhibitors)

RN 944712-03-2 CAPLUS

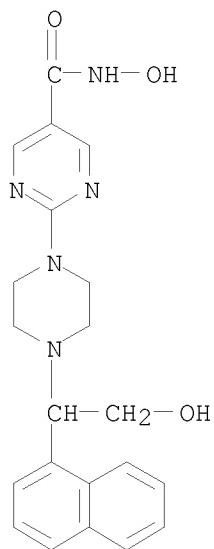
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-(1-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-02-1

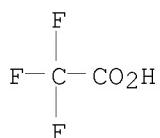
CMF C21 H23 N5 O3

10/513699



CM 2

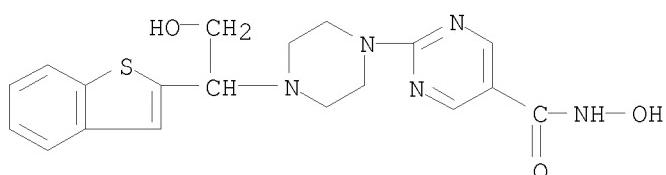
CRN 76-05-1
CMF C₂ H F₃ O₂



RN 944712-05-4 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-(1-benzo[b]thien-2-yl-2-hydroxyethyl)-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

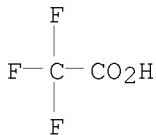
CRN 944712-04-3
CMF C₁₉ H₂₁ N₅ O₃ S



CM 2

10/513699

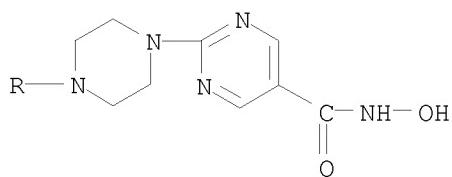
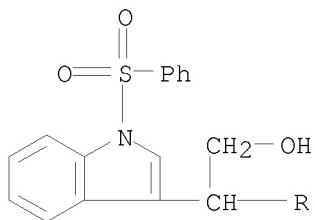
CRN 76-05-1
CMF C2 H F3 O2



RN 944712-07-6 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-[1-(phenylsulfonyl)-1H-indol-3-yl]ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

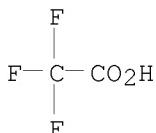
CM 1

CRN 944712-06-5
CMF C25 H26 N6 O5 S



CM 2

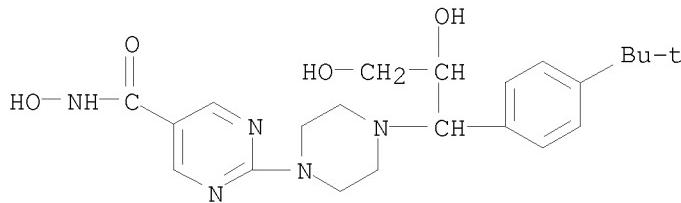
CRN 76-05-1
CMF C2 H F3 O2



RN 944712-09-8 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[1-[4-(1,1-dimethylethyl)phenyl]-2,3-

10/513699

dihydroxypropyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



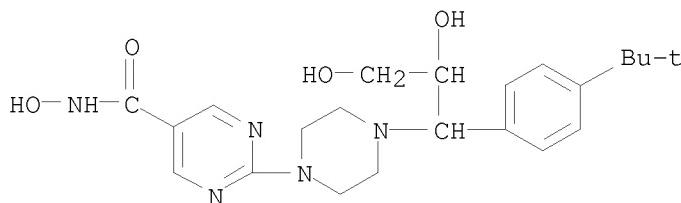
RN 944712-10-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1)
(CA INDEX NAME)

CM 1

CRN 944712-09-8

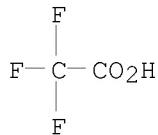
CMF C22 H31 N5 O4



CM 2

CRN 76-05-1

CMF C2 H F3 O2



RN 944712-12-3 CAPLUS

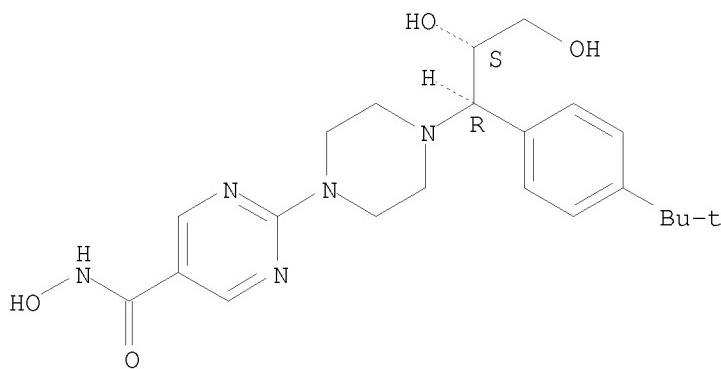
CN 5-Pyrimidinecarboxamide, 2-[4-[(1R,2S)-1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?)
(CA INDEX NAME)

CM 1

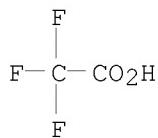
CRN 944712-11-2

CMF C22 H31 N5 O4

Absolute stereochemistry.

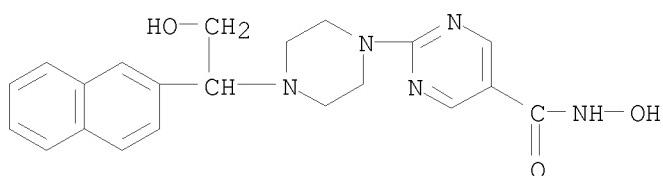


CM 2

CRN 76-05-1
CMF C2 H F3 O2

RN 944712-14-5 CAPLUS
 CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-(2-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

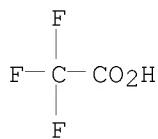
CM 1

CRN 944712-13-4
CMF C21 H23 N5 O3

CM 2

CRN 76-05-1
CMF C2 H F3 O2

10/513699



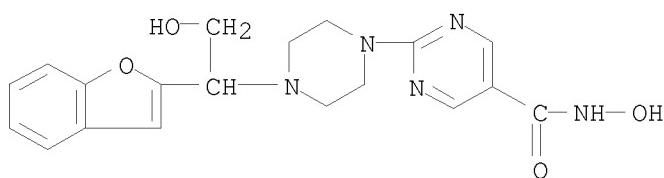
RN 944712-16-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-(2-benzofuranyl)-2-hydroxyethyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-15-6

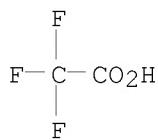
CMF C19 H21 N5 O4



CM 2

CRN 76-05-1

CMF C2 H F3 O2



RN 944712-18-9 CAPLUS

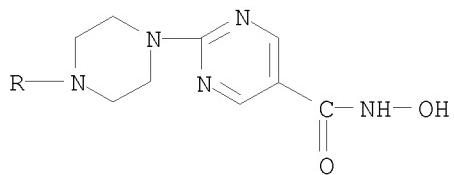
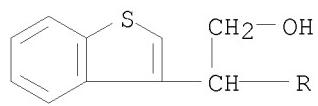
CN 5-Pyrimidinecarboxamide, 2-[4-(1-benzo[b]thien-3-yl-2-hydroxyethyl)-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-17-8

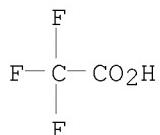
CMF C19 H21 N5 O3 S

10/513699



CM 2

CRN 76-05-1
CMF C2 H F3 O2



REFERENCE COUNT:

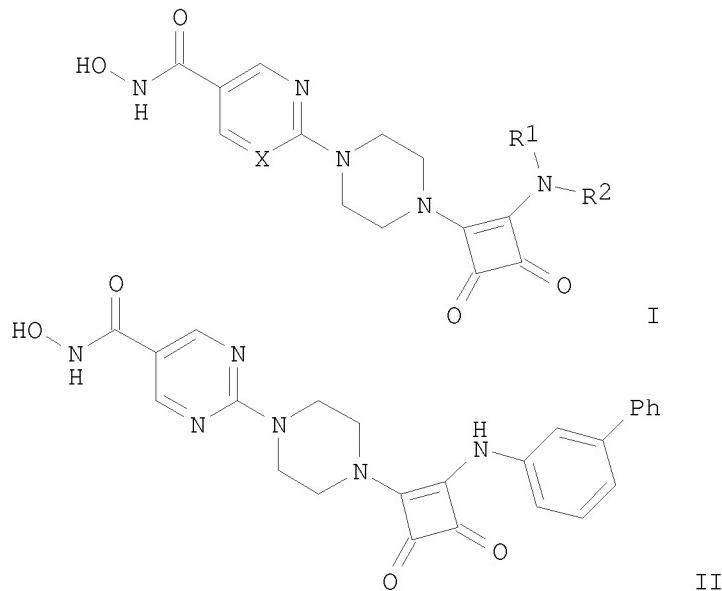
3

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/513699

L11 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:485854 CAPLUS
DOCUMENT NUMBER: 146:482095
TITLE: Preparation of squaric acid derivatives as histone deacetylase (HDAC) inhibitors for the treatment of proliferative diseases
INVENTOR(S): Van Emelen, Kristof
PATENT ASSIGNEE(S): Janssen Pharmaceutica N. V., Belg.
SOURCE: PCT Int. Appl., 37pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|--------|------------|-----------------|------------|
| WO 2007048767 | A1 | 20070503 | WO 2006-EP67656 | 20061023 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| AU 2006307918 | A1 | 20070503 | AU 2006-307918 | 20061023 |
| CA 2623360 | A1 | 20070503 | CA 2006-2623360 | 20061023 |
| EP 1943232 | A1 | 20080716 | EP 2006-807466 | 20061023 |
| R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS | | | | |
| PRIORITY APPLN. INFO.: | | | EP 2005-110080 | A 20051027 |
| | | | WO 2006-EP67656 | W 20061023 |
| OTHER SOURCE(S): | MARPAT | 146:482095 | | |
| GI | | | | |



AB Title compds. I [wherein X = N or CH; R1, R2 = H, alkyl, Ph, etc.;] or N-oxides, pharmaceutically acceptable salts and stereoisomers thereof were prepared as histone deacetylase (HDAC) inhibitors. For instance, successive condensation of 3,4-diethoxy-3-cyclobutene-1,2-dione with 3-aminobiphenyl and 2-(1-piperazinyl)pyrimidine-5-carboxylic acid Et ester, ester hydrolysis, condensation of the resultant acid with NH₂O-THP, and deprotection with TFA gave hydroxamic acid II. This compds. showed inhibition against HDAC with pIC₅₀ = 7.7. The invented compds. are useful for the treatment of proliferative diseases.

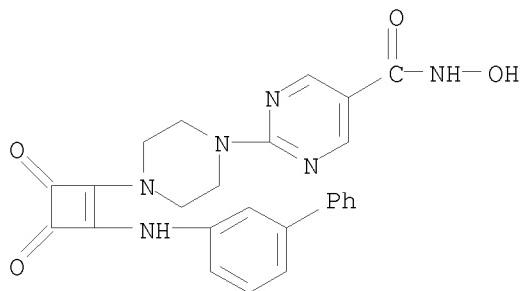
IT 935670-93-2P 935670-95-4P 935670-97-6P
 935670-99-8P 935671-01-5P 935671-03-7P
 935671-05-9P 935671-07-1P 935671-09-3P
 935671-11-7P 935671-13-9P 935671-15-1P
 935671-17-3P 935671-19-5P 935671-21-9P
 935671-23-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of squaric acid derivs. as histone deacetylase (HDAC) inhibitors for treatment of proliferative diseases)

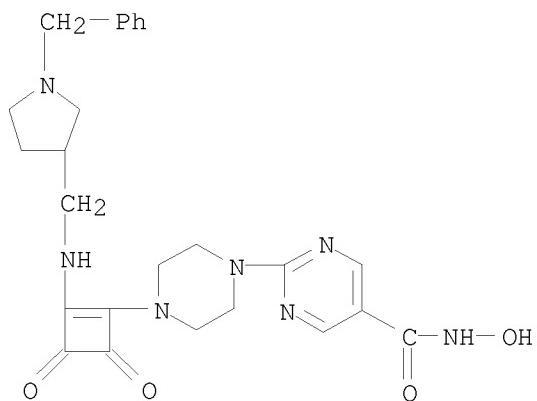
RN 935670-93-2 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-([1,1'-biphenyl]-3-ylamino)-3,4-dioxo-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



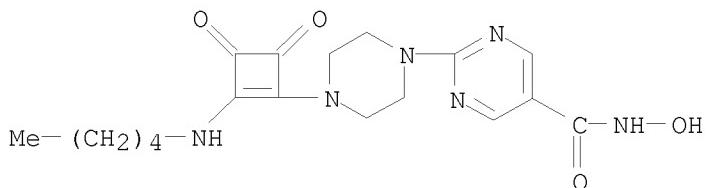
RN 935670-95-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[(1-(phenylmethyl)-3-pyrrolidinyl]methyl]amino]-1-cyclobuten-1-yl]-1-piperazinyl-N-hydroxymethylcarboxamide (CA INDEX NAME)



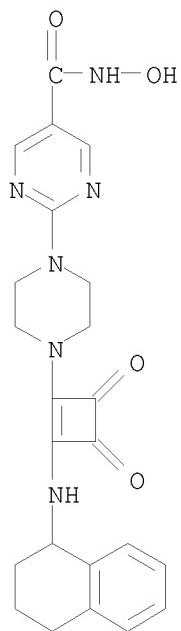
RN 935670-97-6 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-(pentylamino)-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxymethylcarboxamide (CA INDEX NAME)



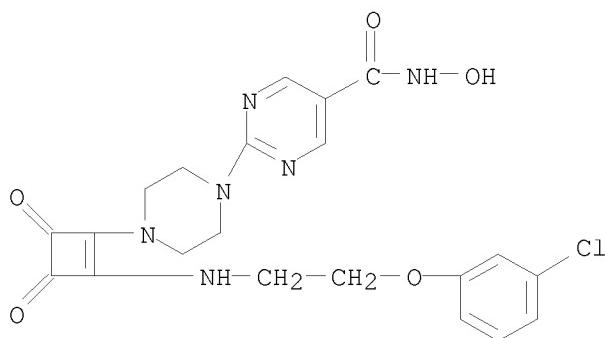
RN 935670-99-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[(1,2,3,4-tetrahydro-1-naphthalenyl)amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxymethylcarboxamide (CA INDEX NAME)



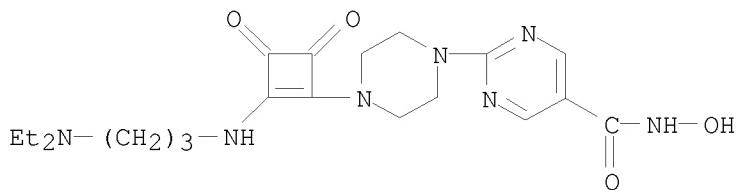
RN 935671-01-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-[(2-(3-chlorophenoxy)ethyl]amino]-3,4-dioxo-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



RN 935671-03-7 CAPLUS

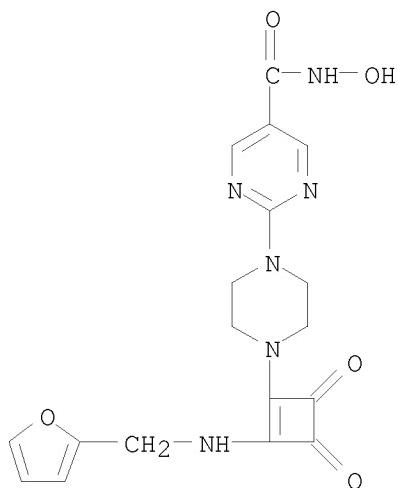
CN 5-Pyrimidinecarboxamide, 2-[4-[2-[(3-(diethylamino)propyl]amino]-3,4-dioxo-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



10/513699

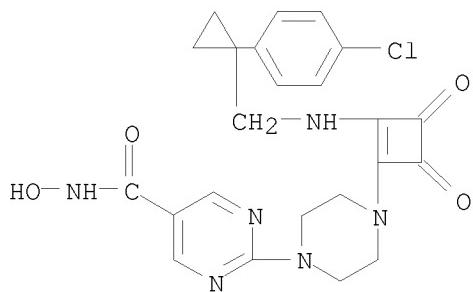
RN 935671-05-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-[(2-furanyl methyl)amino]-3,4-dioxo-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



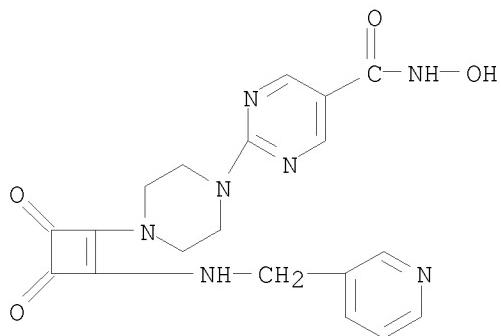
RN 935671-07-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-[[[1-(4-chlorophenyl)cyclopropyl]methyl]amino]-3,4-dioxo-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



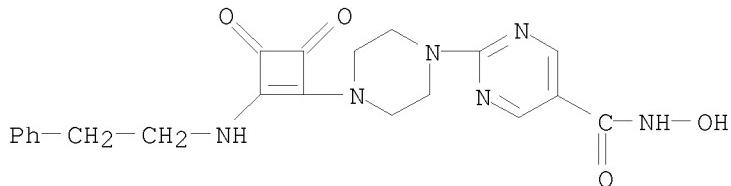
RN 935671-09-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[(3-pyridinylmethyl)amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



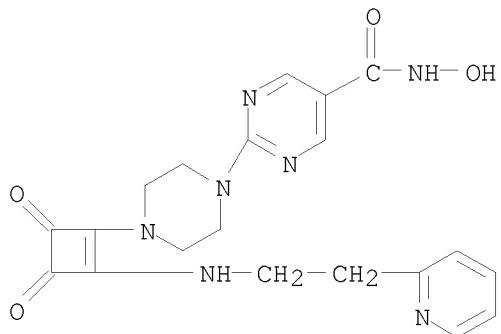
RN 935671-11-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[(2-phenylethyl)amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



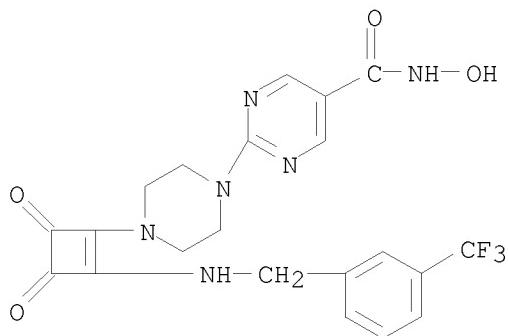
RN 935671-13-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[(2-(2-pyridinyl)ethyl)amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

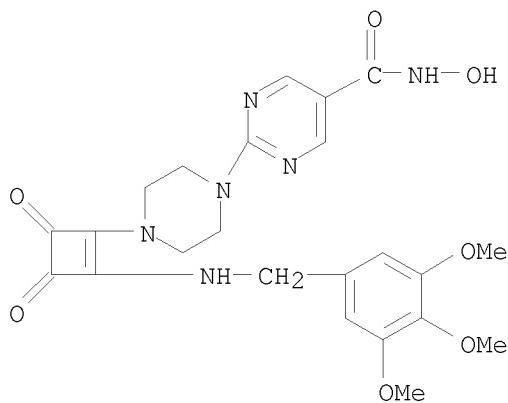


RN 935671-15-1 CAPLUS

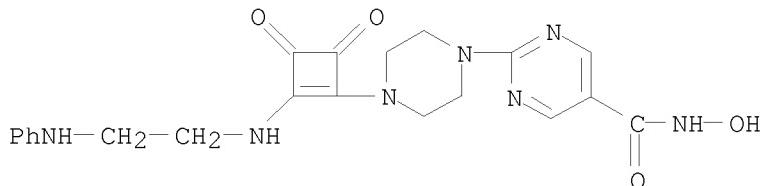
CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[[[3-(trifluoromethyl)phenyl]methyl]amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



RN 935671-17-3 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[(3,4,5-trimethoxyphenyl)methyl]amino]-1-cyclobuten-1-yl]-1-piperazinyl-N-hydroxy- (CA INDEX NAME)



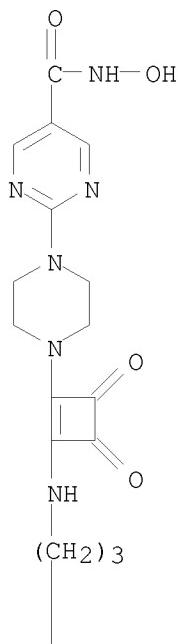
RN 935671-19-5 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[(2-phenylamino)ethyl]amino]-1-cyclobuten-1-yl]-1-piperazinyl-N-hydroxy- (CA INDEX NAME)



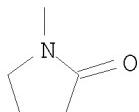
RN 935671-21-9 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[(3-(2-oxo-1-pyrrolidinyl)propyl)amino]-1-cyclobuten-1-yl]-1-piperazinyl-N-hydroxy- (CA INDEX NAME)

10/513699

PAGE 1-A

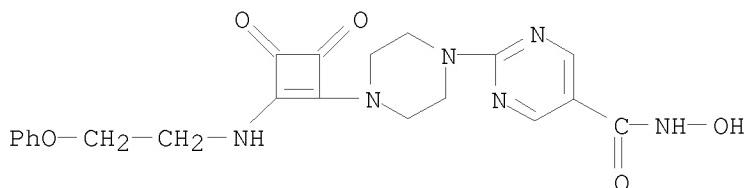


PAGE 2-A



RN 935671-23-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[(2-phenoxyethyl)amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



REFERENCE COUNT:

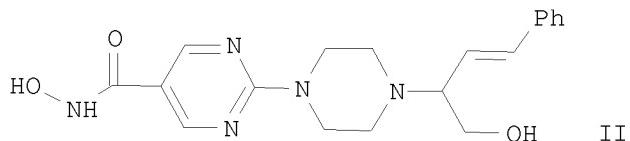
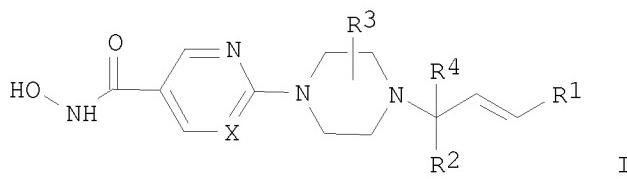
10

THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN
 ACCESSION NUMBER: 2006:101446 CAPLUS
 DOCUMENT NUMBER: 144:192266
 TITLE: Preparation of substituted propenyl piperazine derivatives as novel inhibitors of histone deacetylase
 INVENTOR(S): Van Brandt, Sven Franciscus Anna; Van Emelen, Kristof; Angibaud, Patrick Rene; Marconnet-Decrane, Laurence Francoise Bernadette; Arts, Janine
 PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.
 SOURCE: PCT Int. Appl., 67 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|------------|
| WO 2006010749 | A2 | 20060202 | WO 2005-EP53611 | 20050725 |
| WO 2006010749 | A3 | 20060608 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ,
LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA,
NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK,
SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU,
ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM | | | | |
| AU 2005266311 | A1 | 20060202 | AU 2005-266311 | 20050725 |
| CA 2572971 | A1 | 20060202 | CA 2005-2572971 | 20050725 |
| EP 1776358 | A2 | 20070425 | EP 2005-777776 | 20050725 |
| R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL,
BA, HR, MK, YU | | | | |
| CN 1993356 | A | 20070704 | CN 2005-80025487 | 20050725 |
| JP 2008508234 | T | 20080321 | JP 2007-523072 | 20050725 |
| BR 2005013891 | A | 20080520 | BR 2005-13891 | 20050725 |
| KR 2007043978 | A | 20070426 | KR 2007-701641 | 20070123 |
| US 20070135424 | A1 | 20070614 | US 2007-626215 | 20070123 |
| IN 2007DN00658 | A | 20070803 | IN 2007-DN658 | 20070124 |
| MX 200701119 | A | 20070315 | MX 2007-1119 | 20070126 |
| NO 2007001117 | A | 20070227 | NO 2007-1117 | 20070227 |
| PRIORITY APPLN. INFO.: | | | EP 2004-77171 | A 20040728 |
| | | | US 2004-592357P | P 20040729 |
| | | | WO 2005-EP53611 | W 20050725 |

OTHER SOURCE(S): CASREACT 144:192266; MARPAT 144:192266
 GI



AB Substituted propenyl piperazine derivs. I, wherein X is independently N or CH; R1 is Ph, naphthalenyl or heterocyclyl; wherein each of said Ph or naphthalenyl is optionally substituted with one or two substituents each independently selected from halo, alkyl, alkyloxy, poly-halo-alkyl, aryl, hydroxy, cyano, amino, alkylcarbonylamino, alkylsulfonylamino, hydroxycarbonyl, alkyloxycarbonyl, hydroxyalkyl, alkyloxymethyl, aminomethyl, alkylaminomethyl, alkylcarbonylaminomethyl, alkylsulfonylaminomethyl, aminosulfonyl, alkylaminosulfonyl or heterocyclyl; R2 is hydrogen, -CH₂R₅, trifluoromethyl, -C(O)-R₆, or -CH-NR₇R₈; wherein each R₅ is independently hydrogen, hydroxy, alkyloxy, alkyloxyalkyloxy, alkylcarbonyloxy, piperazinyl, N-methylpiperazinyl, morpholinyl, thiomorpholinyl, imidazolyl or triazolyl; each R₆ is independently hydroxy, alkyloxy, amino or mono- or di(alkyl)amino, cycloalkylamino, hydroxyalkylamino, piperazinyl, N-methylpiperazinyl, morpholinyl or thiomorpholinyl; each R₇ and R₈ are independently hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, or mono- or di(alkyl)aminosulfonyl; R₃ is hydrogen, hydroxymethyl, aminomethyl or mono- or di(alkyl)aminomethyl; R₄ is hydrogen or alkyl; were prepared and having histone deacetylase inhibiting enzymic activity and to inhibit proliferative conditions, such as cancer and psoriasis. Thus, propenyl piperazine derivative II was prepared and tested in vitro and in nude mice as inhibitor of histone deacetylase and was better than R306465 after oral administration. P21 enzyme linked immunosorbent assay has been applied to determine the p21 protein expression level in human A2780 ovarian carcinoma cells. In vitro assay for inhibition of histone deacetylase is reported. P21 induction was measured as the consequence of DNA damage or as the consequence of histone deacetylase inhibition. Antiproliferative activity of title compds. was determined on A2780 cells (neg. log value of the IC₅₀, pIC₅₀ = 7.9-8.2).

IT 875138-85-5P 875138-87-7P 875138-88-8P
 875138-89-9P 875138-90-2P 875138-91-3P
 875138-93-5P 875138-94-6P 875138-98-0P
 875139-00-7P 875139-02-9P 875139-04-1P
 875139-06-3P 875139-07-4P 875139-09-6P
 875139-11-0P 875139-13-2P 875139-14-3P
 875139-15-4P 875139-17-6P 875139-19-8P
 875139-20-1P 875139-21-2P 875139-23-4P
 875139-24-5P 875139-25-6P 875139-26-7P
 875139-27-8P 875139-28-9P 875139-29-0P
 875139-30-3P 875139-31-4P 875139-69-8P

10/513699

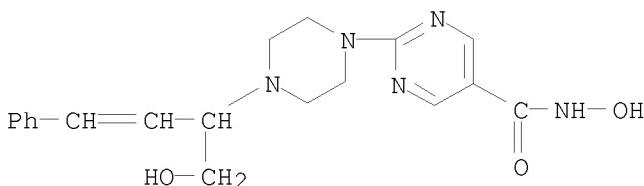
875139-70-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of substituted propenyl piperazine derivs. as novel inhibitors of histone deacetylase)

RN 875138-85-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)



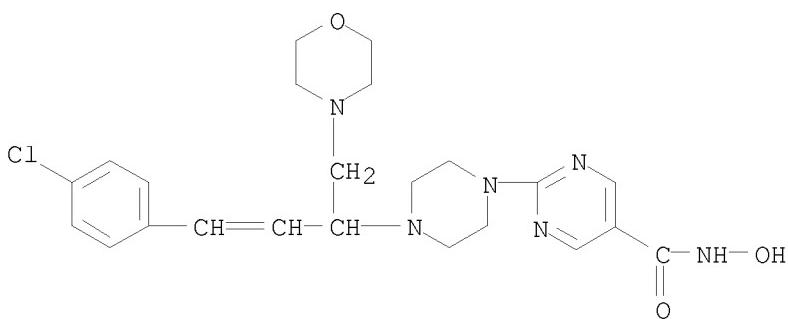
RN 875138-87-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-chlorophenyl)-1-(4-morpholinylmethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-86-6

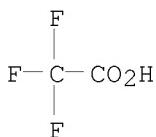
CMF C23 H29 Cl N6 O3



CM 2

CRN 76-05-1

CMF C2 H F3 O2

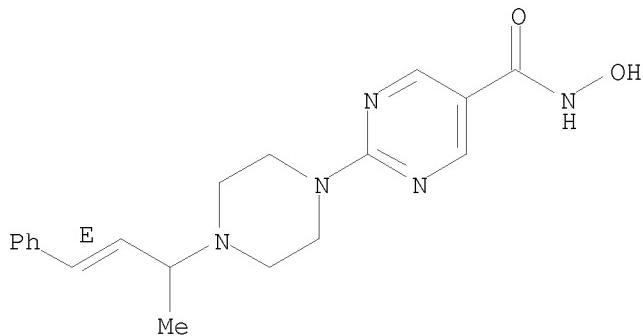


10/513699

RN 875138-88-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-methyl-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Double bond geometry as shown.



RN 875138-89-9 CAPLUS

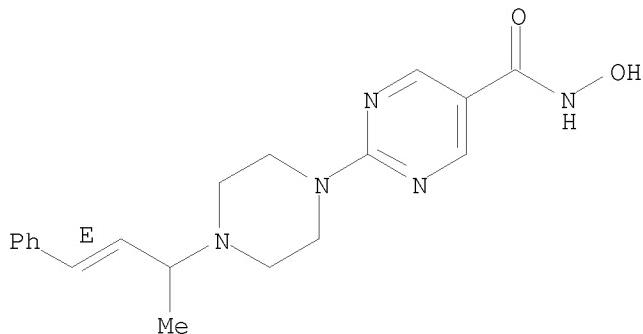
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-methyl-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-88-8

CMF C19 H23 N5 O2

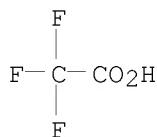
Double bond geometry as shown.



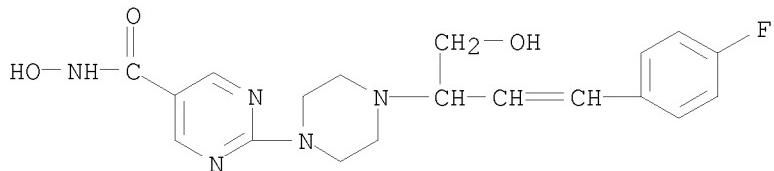
CM 2

CRN 76-05-1

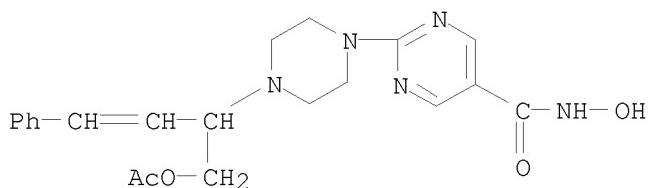
CMF C2 H F3 O2



RN 875138-90-2 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



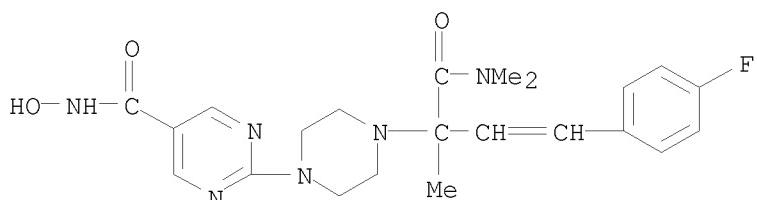
RN 875138-91-3 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(acetyloxy)methyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



RN 875138-93-5 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(dimethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

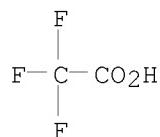
CRN 875138-92-4
 CMF C22 H27 F N6 O3



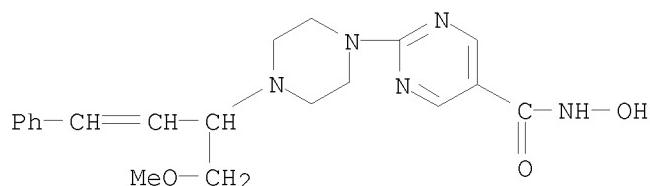
CM 2

10/513699

CRN 76-05-1
CMF C2 H F3 O2



RN 875138-94-6 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(methoxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

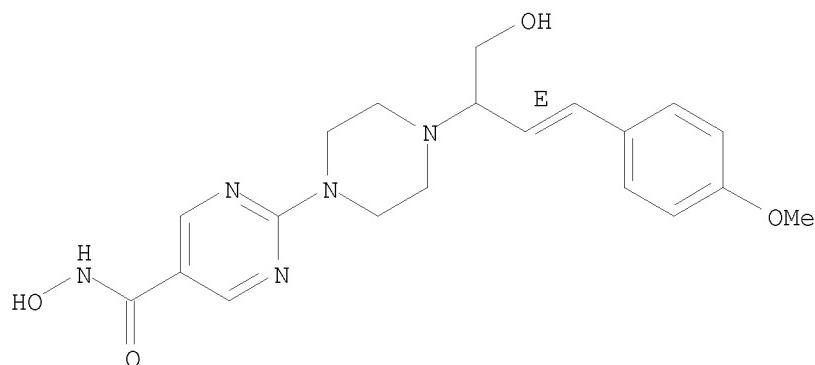


RN 875138-98-0 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-(hydroxymethyl)-3-(4-methoxyphenyl)-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-97-9
CMF C20 H25 N5 O4

Double bond geometry as shown.

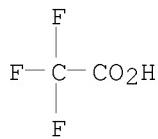


CM 2

CRN 76-05-1

10/513699

CMF C2 H F3 O2



RN 875139-00-7 CAPLUS

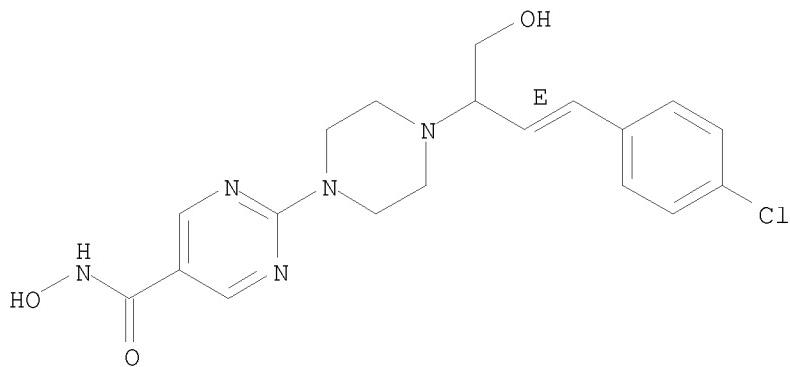
CN 5-Pyrimidinecarboxamide, 2-[4-[(2E)-3-(4-chlorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-99-1

CMF C19 H22 Cl N5 O3

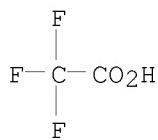
Double bond geometry as shown.



CM 2

CRN 76-05-1

CMF C2 H F3 O2



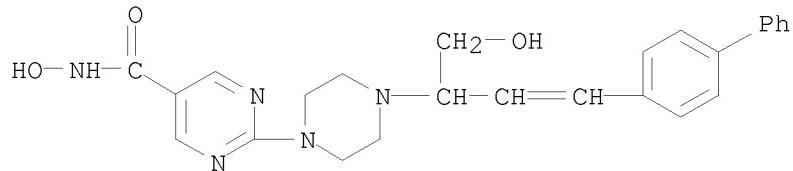
RN 875139-02-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-[1,1'-biphenyl]-4-yl-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

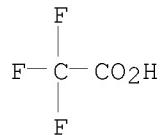
10/513699

CRN 875139-01-8
CMF C25 H27 N5 O3



CM 2

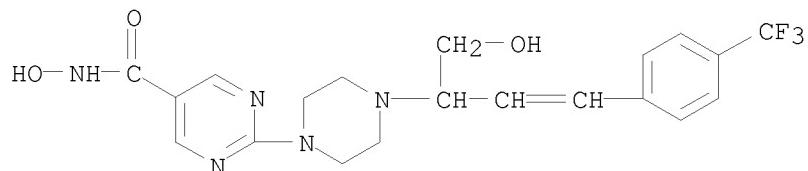
CRN 76-05-1
CMF C2 H F3 O2



RN 875139-04-1 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(hydroxymethyl)-3-[4-(trifluoromethyl)phenyl]-2-propen-1-yl]piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

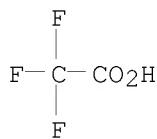
CRN 875139-03-0
CMF C20 H22 F3 N5 O3



CM 2

CRN 76-05-1
CMF C2 H F3 O2

10/513699



RN 875139-06-3 CAPLUS

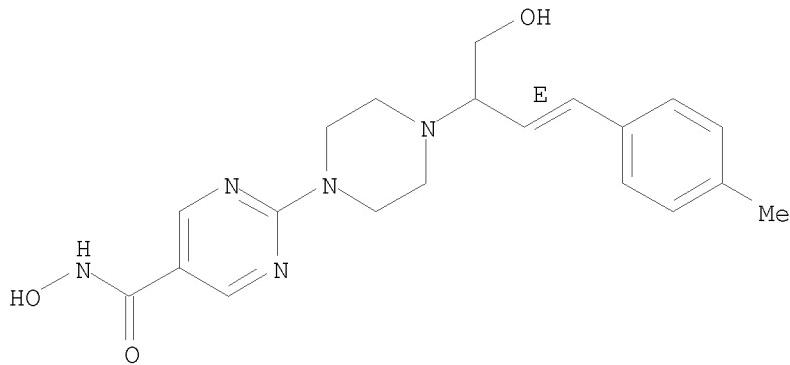
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-(hydroxymethyl)-3-(4-methylphenyl)-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-05-2

CMF C20 H25 N5 O3

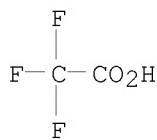
Double bond geometry as shown.



CM 2

CRN 76-05-1

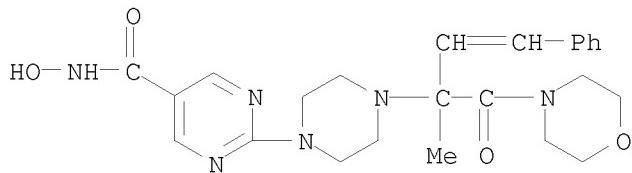
CMF C2 H F3 O2



RN 875139-07-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(1-methyl-1-(4-morpholinylcarbonyl)-3-phenyl-2-propen-1-yl)-1-piperazinyl]- (CA INDEX NAME)

10/513699



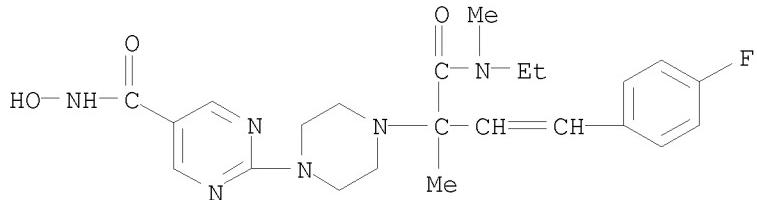
RN 875139-09-6 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(ethylmethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-08-5

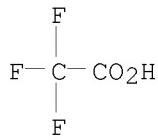
CMF C23 H29 F N6 O3



CM 2

CRN 76-05-1

CMF C2 H F3 O2



RN 875139-11-0 CAPLUS

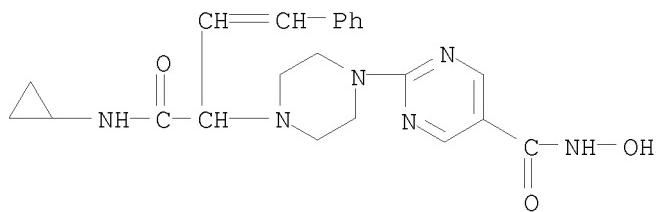
CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(cyclopropylamino)carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-10-9

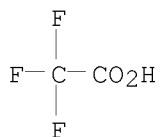
CMF C22 H26 N6 O3

10/513699



CM 2

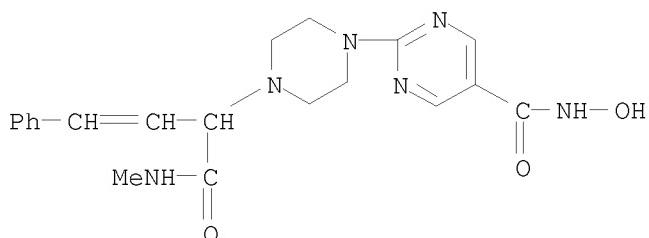
CRN 76-05-1
CMF C2 H F3 O2



RN 875139-13-2 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-[(methylamino)carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

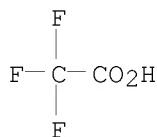
CRN 875139-12-1
CMF C20 H24 N6 O3



CM 2

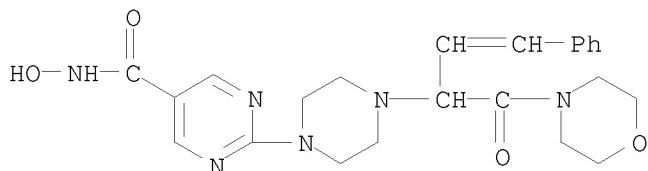
CRN 76-05-1
CMF C2 H F3 O2

10/513699



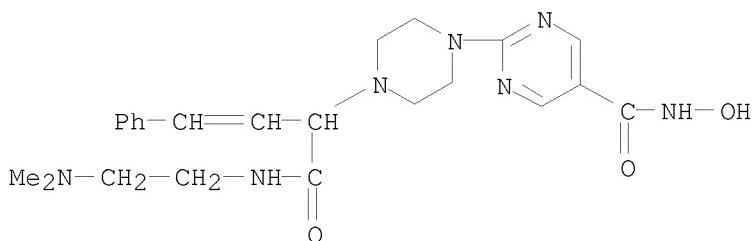
RN 875139-14-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(4-morpholinylcarbonyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)



RN 875139-15-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[[(2-(dimethylamino)ethyl]amino]carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



RN 875139-17-6 CAPLUS

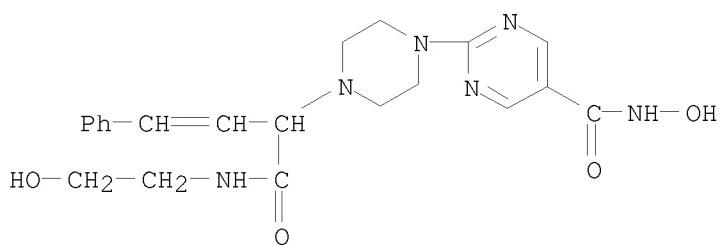
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-[[(2-hydroxyethyl)amino]carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-16-5

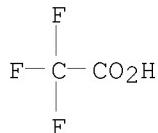
CMF C21 H26 N6 O4

10/513699



CM 2

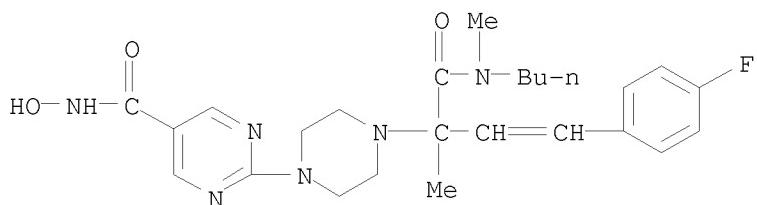
CRN 76-05-1
CMF C2 H F3 O2



RN 875139-19-8 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[(butylmethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

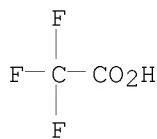
CRN 875139-18-7
CMF C25 H33 F N6 O3



CM 2

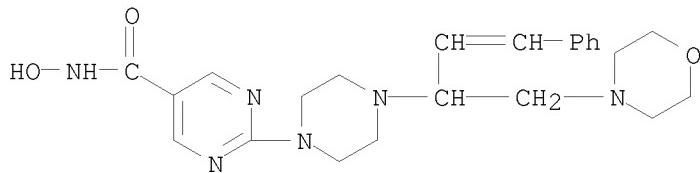
CRN 76-05-1
CMF C2 H F3 O2

10/513699



RN 875139-20-1 CAPLUS

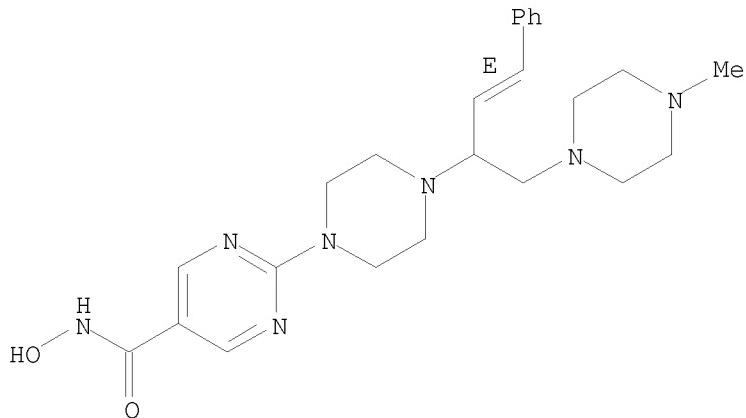
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(4-morpholinylmethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)



RN 875139-21-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[((2E)-1-[(4-methyl-1-piperazinyl)methyl]-3-phenyl-2-propen-1-yl)-1-piperazinyl]- (CA INDEX NAME)

Double bond geometry as shown.



RN 875139-23-4 CAPLUS

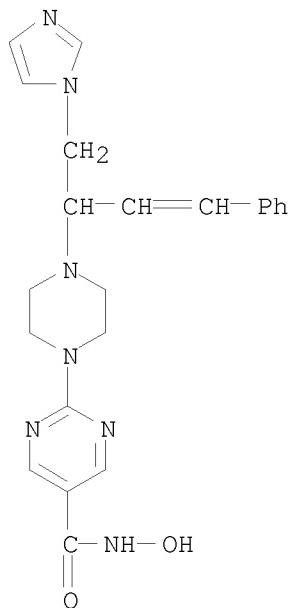
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(1H-imidazol-1-ylmethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-22-3

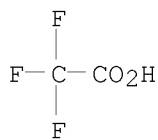
CMF C22 H25 N7 O2

10/513699

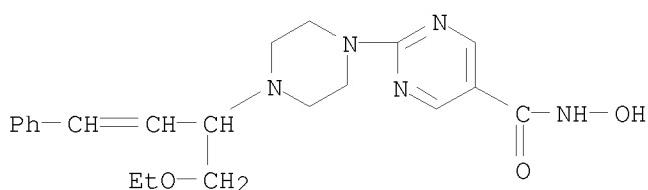


CM 2

CRN 76-05-1
CMF C2 H F3 O2



RN 875139-24-5 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[1-(ethoxymethyl)-3-phenyl-2-propenyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

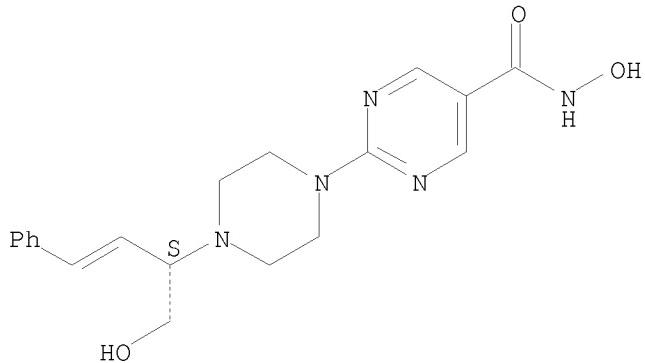


RN 875139-25-6 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(1S)-1-(hydroxymethyl)-3-phenyl-2-propenyl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

10/513699

Double bond geometry unknown.

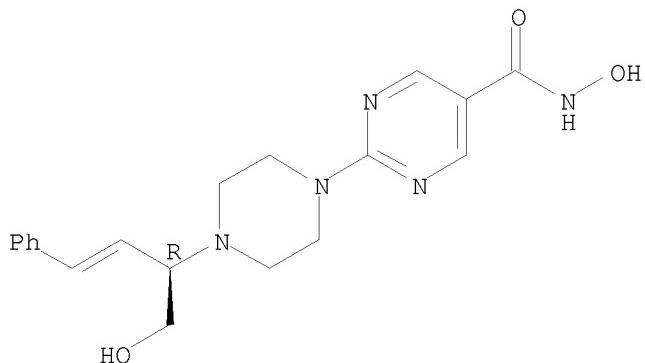


RN 875139-26-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(1R)-1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

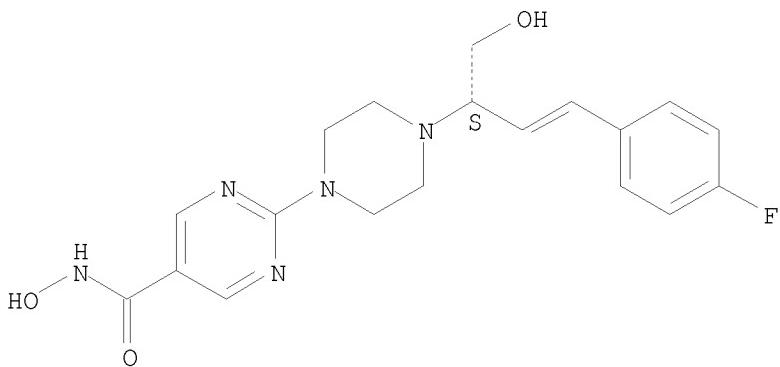


RN 875139-27-8 CAPLUS

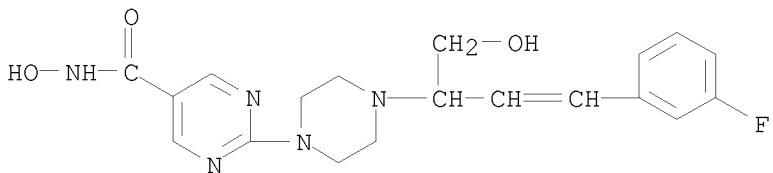
CN 5-Pyrimidinecarboxamide, 2-[4-[(1S)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.

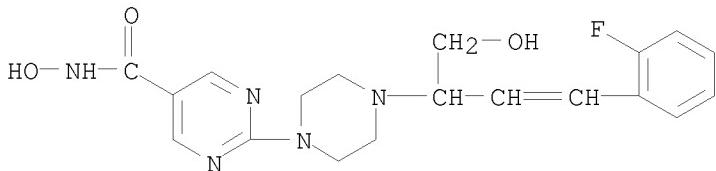
Double bond geometry unknown.



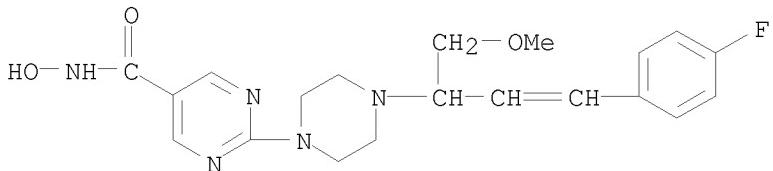
RN 875139-28-9 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[3-(3-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



RN 875139-29-0 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[3-(2-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



RN 875139-30-3 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-fluorophenyl)-1-(methoxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

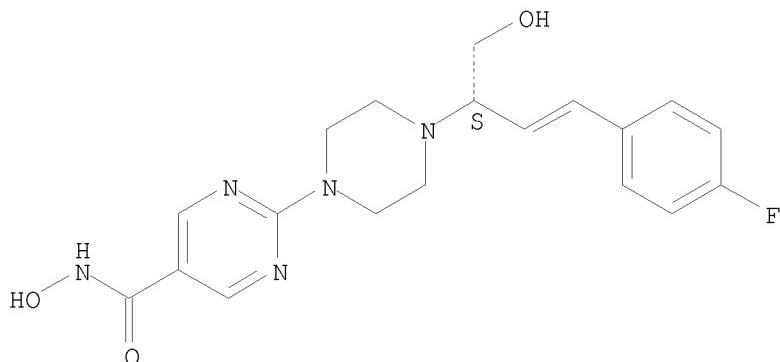


RN 875139-31-4 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-fluorophenyl)-1-(hydroxymethyl)-2-

10/513699

propen-1-yl]-1-piperazinyl]-N-hydroxy-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

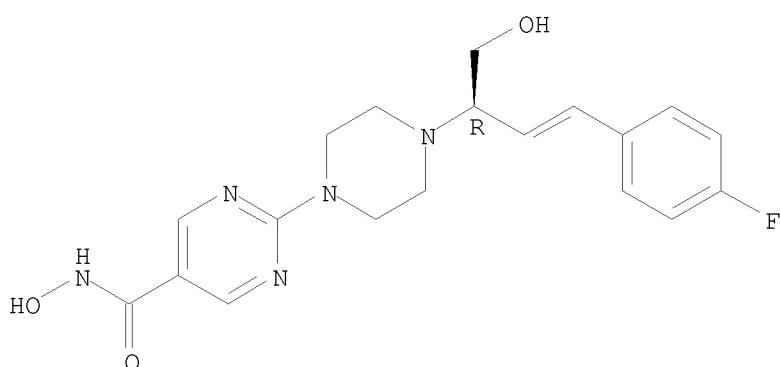


● HCl

RN 875139-69-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

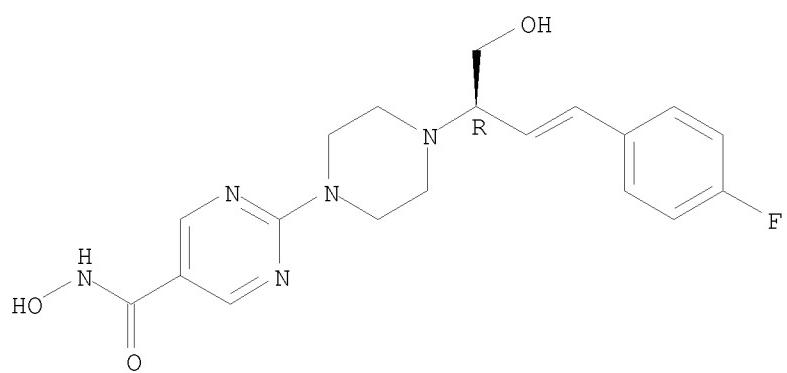


RN 875139-70-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

10/513699

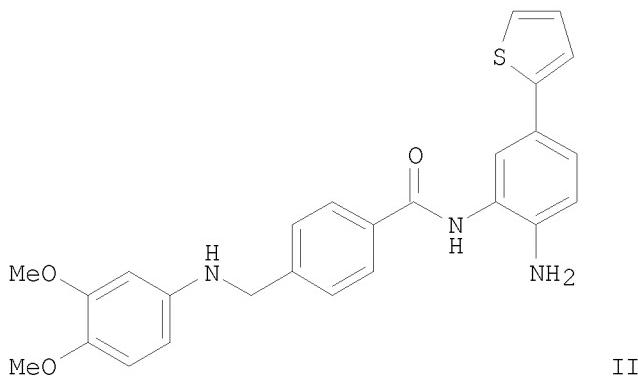
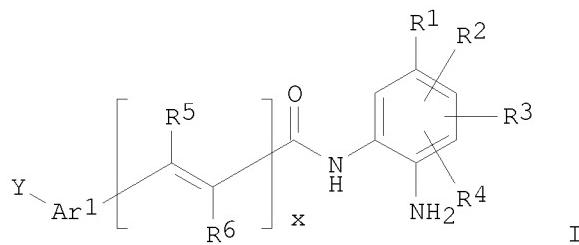


● HCl

10/513699

L11 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:300395 CAPLUS
DOCUMENT NUMBER: 142:355054
TITLE: Preparation of amide derivatives as inhibitors of histone deacetylase
INVENTOR(S): Moradei, Oscar; Paquin, Isabelle; Leit, Silvana;
Frechette, Sylvie; Vaisburg, Arkadii; Besterman,
Jeffrey M.; Tessier, Pierre; Mallais, Tammy C.
PATENT ASSIGNEE(S): Methylgene, Inc., Can.
SOURCE: PCT Int. Appl., 559 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|--|----------|------------------|-------------|
| WO 2005030705 | A1 | 20050407 | WO 2004-US31591 | 20040924 |
| WO 2005030705 | A9 | 20060420 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG | | | | |
| AU 2004276337 | A1 | 20050407 | AU 2004-276337 | 20040924 |
| CA 2539117 | A1 | 20050407 | CA 2004-2539117 | 20040924 |
| EP 1663953 | A1 | 20060607 | EP 2004-789074 | 20040924 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR | | | | |
| CN 1882529 | A | 20061220 | CN 2004-80034571 | 20040924 |
| JP 2007506785 | T | 20070322 | JP 2006-528279 | 20040924 |
| US 20080132459 | A1 | 20080605 | US 2006-574088 | 20060323 |
| JP 2008094847 | A | 20080424 | JP 2007-281356 | 20071030 |
| PRIORITY APPLN. INFO.: | | | US 2003-505884P | P 20030924 |
| | | | US 2003-532973P | P 20031229 |
| | | | US 2004-561082P | P 20040409 |
| | | | JP 2006-528279 | A3 20040924 |
| | | | WO 2004-US31591 | W 20040924 |
| OTHER SOURCE(S): GI | CASREACT 142:355054; MARPAT 142:355054 | | | |



AB Title compds. I [Ar1 = (un)saturated-, (un)substituted-mono or fused poly-cyclic hydrocarbyl optionally containing 1-4 heteroatoms per ring; R1 = (un)substituted-mono-, -bi-, -tri-cyclic-aryl or -heteroaryl; R2, R3, and R4 independently = H, halo, amino, etc.; R5 and R6 independently = H, alkyl, aryl, etc.; x = 0-1; Y = any pharmaceutically acceptable chemical moiety consisting of 1 to 50 atoms with provisions] and their pharmaceutically acceptable salts, are prepared and disclosed as inhibitors of histone deacetylase. Thus, e.g., II was prepared by Suzuki coupling of 2-bromo-2-nitro-phenylamine (preparation given) with 2-thiopheneboronic acid followed by carbonylation with 4-[3,4-dimethoxy-(phenylamino)-methyl]benzoic acid (preparation given) and subsequent reduction. The inhibitory

capability of I towards antiproliferative activity of histone deacetylase enzyme was evaluated using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay and it revealed that certain compds. of the invention had MTT IC₅₀ values in the range of below 1 up to 20 μM. I as histone deacetylase inhibitors should prove useful in the treatment of diseases such as, but not limited to, cell proliferative disease, protozoal disease, and fungal disease.

IT 603985-82-6P 603985-86-0P 603985-88-2P
603985-90-6P 603985-94-0P 603991-95-3P
603991-96-4P 603992-24-1P 603992-25-2P
603992-26-3P 603992-27-4P 603992-28-5P
604784-81-8P

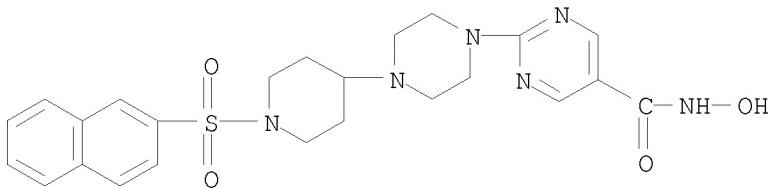
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of amide derivs. as inhibitors of histone deacetylase)

10/513699

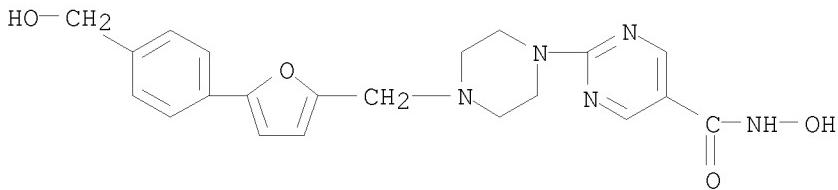
RN 603985-82-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(2-naphthalenylsulfonyl)-4-piperidinyl]-1-piperazinyl]- (CA INDEX NAME)



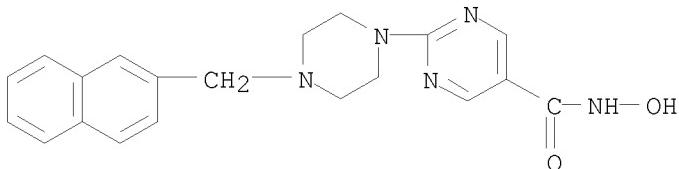
RN 603985-86-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)



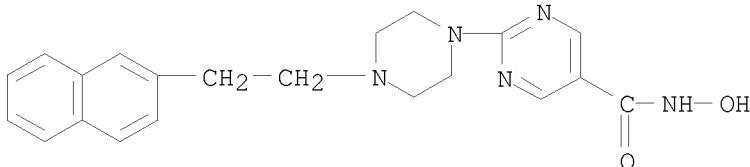
RN 603985-88-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]- (CA INDEX NAME)



RN 603985-90-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]- (CA INDEX NAME)

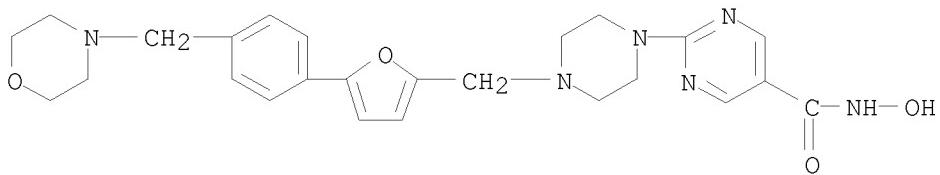


RN 603985-94-0 CAPLUS

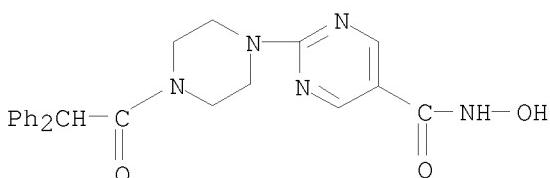
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

10/513699

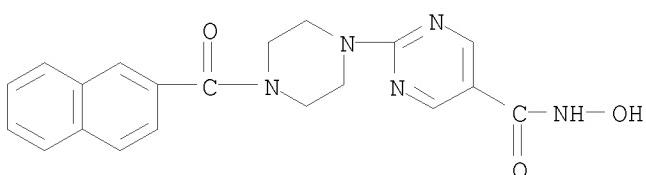
NAME)



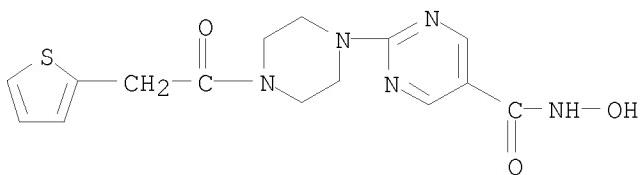
RN 603991-95-3 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



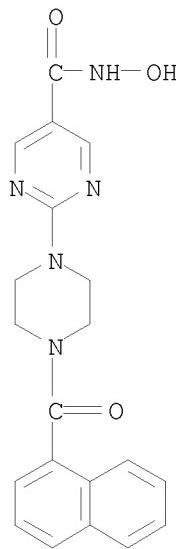
RN 603991-96-4 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



RN 603992-24-1 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-thienylacetyl)-1-piperazinyl]- (CA INDEX NAME)

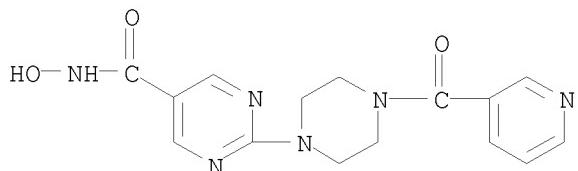


RN 603992-25-2 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



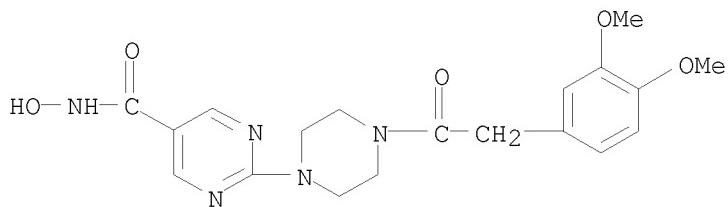
RN 603992-26-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



RN 603992-27-4 CAPLUS

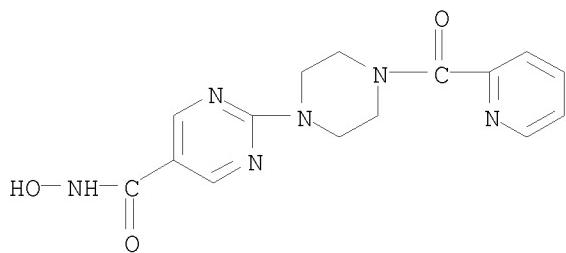
CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



RN 603992-28-5 CAPLUS

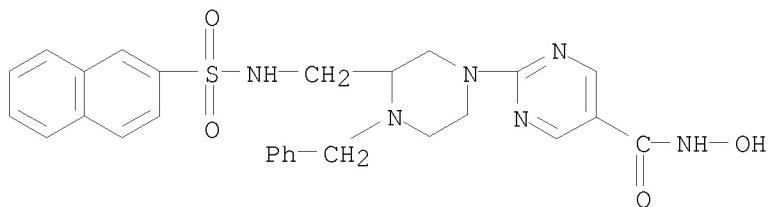
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

10/513699



RN 604784-81-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[3-[(2-naphthalenylsulfonyl)amino]methy]-4-(phenylmethyl)-1-piperazinyl- (CA INDEX NAME)



REFERENCE COUNT:

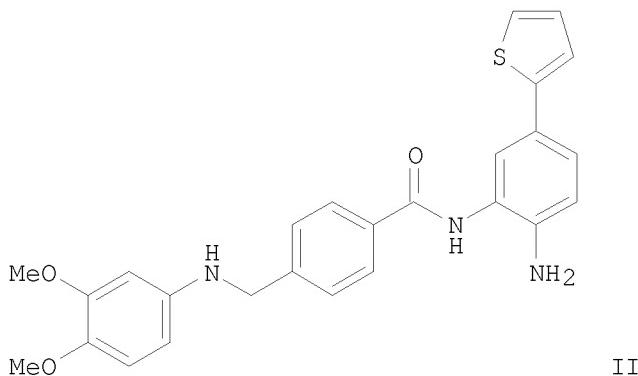
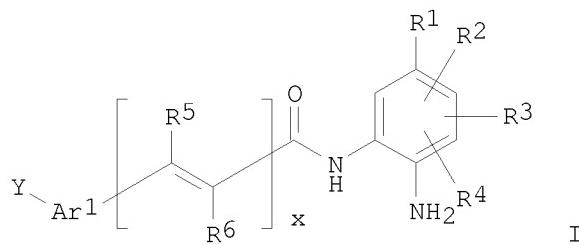
6

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/513699

L11 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:300394 CAPLUS
DOCUMENT NUMBER: 142:373563
TITLE: Preparation of amide derivatives as inhibitors of histone deacetylase
INVENTOR(S): Moradei, Oscar; Paquin, Isabelle; Leit, Silvana;
Frechette, Sylvie; Vaisburg, Arkadii; Besterman,
Jeffrey M.; Tessier, Pierre; Mallais, Tammy C.
PATENT ASSIGNEE(S): Methylgene, Inc., Can.
SOURCE: PCT Int. Appl., 389 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|--|---|---|
| WO 2005030704 | A1 | 20050407 | WO 2004-US31590 | 20040924 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG | | | | |
| JP 2008094847 | A | 20080424 | JP 2007-281356
US 2003-505884P
US 2003-532973P
US 2004-561082P
JP 2006-528279 | 20071030
P 20030924
P 20031229
P 20040409
A3 20040924 |
| PRIORITY APPLN. INFO.: | | | | |
| OTHER SOURCE(S): GI | | CASREACT 142:373563; MARPAT 142:373563 | | |



AB Title compds. I [Ar1 = (un)saturated-, (un)substituted-mono or fused poly-cyclic hydrocarbyl optionally containing 1-4 heteroatoms per ring; R1 = (un)substituted-mono-, -bi-, -tri-cyclic-aryl or -heteroaryl; R2, R3, and R4 independently = H, halo, amino, etc.; R5 and R6 independently = H, alkyl, aryl, etc.; x = 0-1; Y = any pharmaceutically acceptable chemical moiety consisting of 1 to 50 atoms with provisions] and their pharmaceutically acceptable salts, are prepared and disclosed as inhibitors of histone deacetylase. Thus, e.g., II was prepared by Suzuki coupling of 2-bromo-2-nitro-phenylamine (preparation given) with 2-thiopheneboronic acid followed by carbonylation with 4-[3,4-dimethoxy-(phenylamino)-methyl]benzoic acid (preparation given) and subsequent reduction. The inhibitory

capability of I towards antiproliferative activity of histone deacetylase enzyme was evaluated using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay and it revealed that certain compds. of the invention had MTT IC₅₀ values in the range of below 1 up to 20 μM. I as histone deacetylase inhibitors should prove useful in the treatment of diseases such as, but not limited to, cell proliferative disease, protozoal disease, and fungal disease.

IT 603985-82-6P 603985-86-0P 603985-88-2P
603985-90-6P 603985-94-0P 603991-95-3P
603991-96-4P 603992-24-1P 603992-25-2P
603992-26-3P 603992-27-4P 603992-28-5P
604784-81-8P

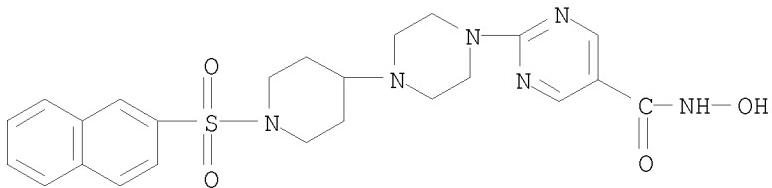
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of amide derivs. as inhibitors of histone deacetylase)

10/513699

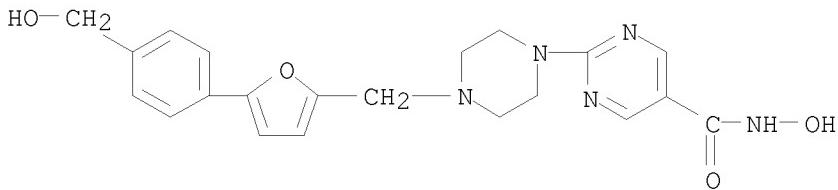
RN 603985-82-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(2-naphthalenylsulfonyl)-4-piperidinyl]-1-piperazinyl]- (CA INDEX NAME)



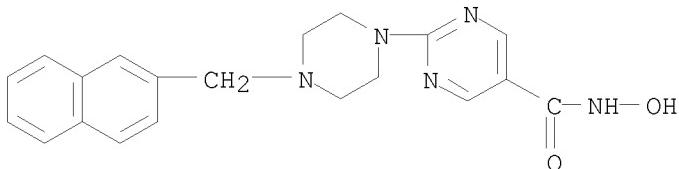
RN 603985-86-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)



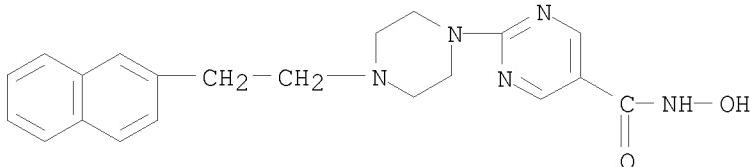
RN 603985-88-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]- (CA INDEX NAME)



RN 603985-90-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]- (CA INDEX NAME)

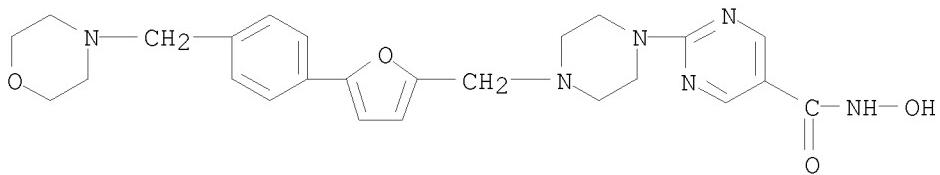


RN 603985-94-0 CAPLUS

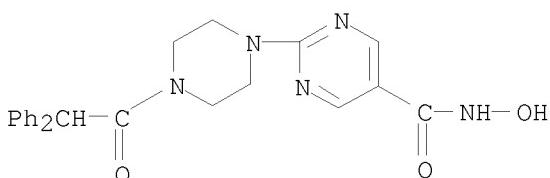
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

10/513699

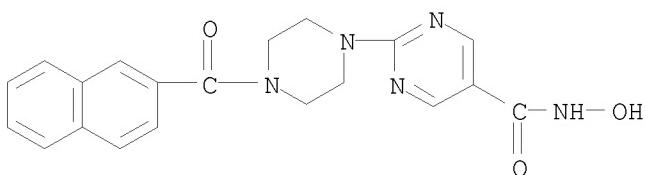
NAME)



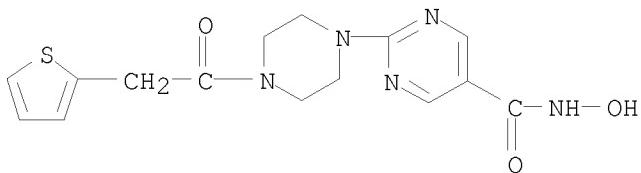
RN 603991-95-3 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



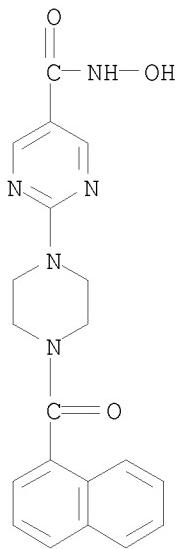
RN 603991-96-4 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



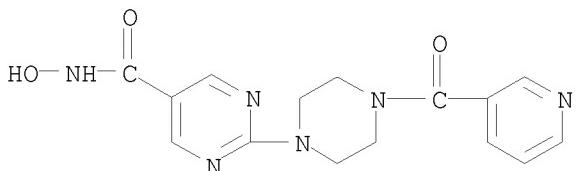
RN 603992-24-1 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-thienylacetyl)-1-piperazinyl]- (CA INDEX NAME)



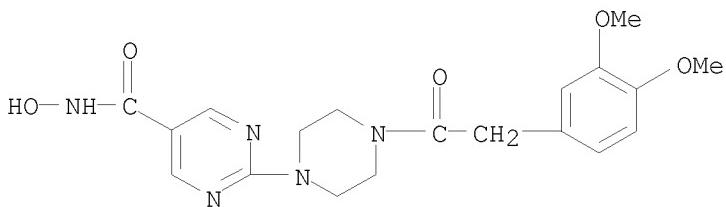
RN 603992-25-2 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



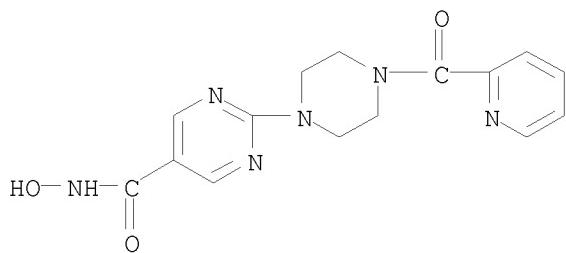
RN 603992-26-3 CAPLUS
 CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



RN 603992-27-4 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

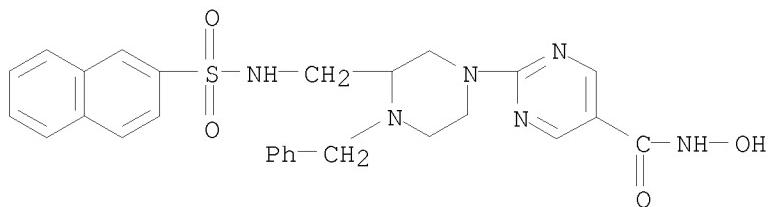


RN 603992-28-5 CAPLUS
 CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



RN 604784-81-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[3-[(2-naphthalenylsulfonyl)amino]methoxy]-4-(phenylmethyl)-1-piperazinyl- (CA INDEX NAME)



REFERENCE COUNT:

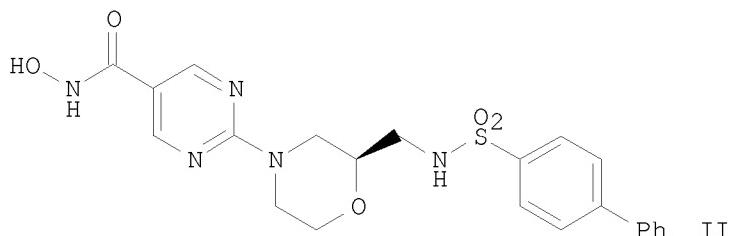
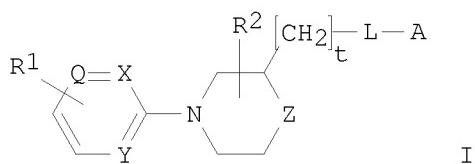
6

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN
 ACCESSION NUMBER: 2003:737757 CAPLUS
 DOCUMENT NUMBER: 139:276911
 TITLE: Preparation of N-(piperazinylmethyl-,
 piperidinylmethyl- and morpholinylmethyl) sulfonamides
 and amides as novel inhibitors of histone deacetylase
 INVENTOR(S): Van Emelen, Kristof
 PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.
 SOURCE: PCT Int. Appl., 69 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 8
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|------------------|-------------|
| WO 2003076438 | A1 | 20030918 | WO 2003-EP2510 | 20030311 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2475766 | A1 | 20030918 | CA 2003-2475766 | 20030311 |
| AU 2003218735 | A1 | 20030922 | AU 2003-218735 | 20030311 |
| EP 1485378 | A1 | 20041215 | EP 2003-711979 | 20030311 |
| EP 1485378 | B1 | 20080618 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| BR 2003007606 | A | 20041221 | BR 2003-7606 | 20030311 |
| CN 1642948 | A | 20050720 | CN 2003-805921 | 20030311 |
| JP 2005526766 | T | 20050908 | JP 2003-574655 | 20030311 |
| NZ 534833 | A | 20060728 | NZ 2003-534833 | 20030311 |
| CN 101007803 | A | 20070801 | CN 2007-10005212 | 20030311 |
| AT 398615 | T | 20080715 | AT 2003-711979 | 20030311 |
| TW 283676 | B | 20070711 | TW 2003-92105285 | 20030312 |
| IN 2004DN02536 | A | 20070413 | IN 2004-DN2536 | 20040831 |
| US 20050165016 | A1 | 20050728 | US 2004-507084 | 20040908 |
| MX 2004PA08795 | A | 20041126 | MX 2004-PA8795 | 20040910 |
| NO 2004004135 | A | 20040929 | NO 2004-4135 | 20040929 |
| PRIORITY APPLN. INFO.: | | | US 2002-363799P | P 20020313 |
| | | | WO 2002-EP14833 | A 20021223 |
| | | | CN 2003-805921 | A3 20030311 |
| | | | WO 2003-EP2510 | W 20030311 |

OTHER SOURCE(S): MARPAT 139:276911
 GI



AB The title compds. [I; t = 0-4; Q, X, Y = N, C; Z = NH, O, CH₂; R₁ = CONR₃R₄, NHCOR₇, CO(alkanediyl)SR₇, etc. (wherein R₃, R₄ = H, OH, alkyl, etc.; R₇ = H, alkyl, alkylcarbonyl, etc.); R₂ = H, OH, NH₂, etc.; L = NR₉CO, NR₉SO₂, NR₉CH₂ (R₉ = H, alkyl, cycloalkyl, etc.); A = (un)substituted Ph, cycloalkyl, pyridyl, etc.], having histone deacetylase inhibiting enzymic activity, were prepared and formulated. E.g., a multi-step synthesis of (+)-II which showed pIC₅₀ of 7.723 against HDAC, was given.

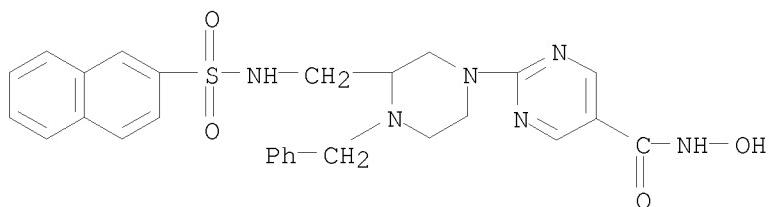
IT 604784-81-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of N-(piperazinylmethyl-, piperidinylmethyl- and morpholinylmethyl) sulfonamides and amides as novel inhibitors of histone deacetylase)

RN 604784-81-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[3-[(2-naphthalenylsulfonyl)amino]methoxy]-4-(phenylmethyl)-1-piperazinyl- (CA INDEX NAME)



REFERENCE COUNT:

2

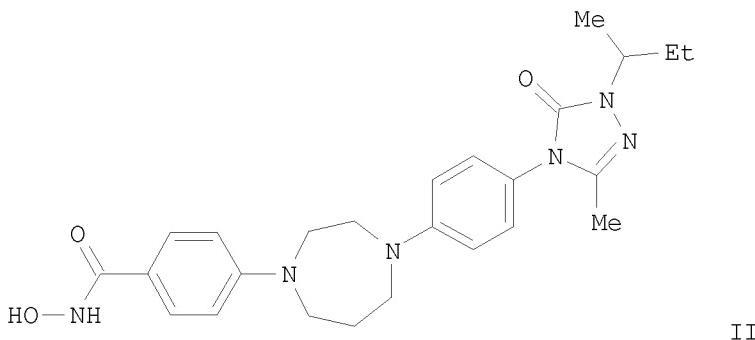
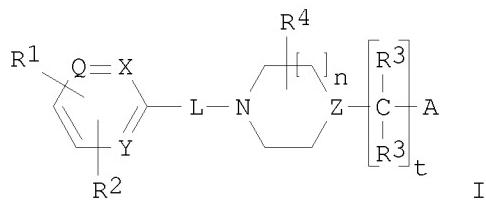
THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN
 ACCESSION NUMBER: 2003:737723 CAPLUS
 DOCUMENT NUMBER: 139:261309
 TITLE: Preparation of N-hydroxy-5-piperazino(piperidino or diazepino)-2-pyrimidinecarboxamides and N-hydroxy-4-piperazino(piperidino or diazepino)benzamides as new inhibitors of histone deacetylase
 INVENTOR(S): Angibaud, Patrick Rene; Pilatte, Isabelle Noeelle Constance; Van Brandt, Sven Franciscus Anna; Roux, Bruno; Ten Holte, Peter; Verdonck, Marc Gustaaf Celine; Meerpoel, Lieven; Dyatkin, Alexey Borisovich Janssen Pharmaceutica N.V., Belg.
 PATENT ASSIGNEE(S):
 SOURCE: PCT Int. Appl., 72 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 8
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|-------------|
| WO 2003076400 | A1 | 20030918 | WO 2003-EP2514 | 20030311 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2475764 | A1 | 20030918 | CA 2003-2475764 | 20030311 |
| AU 2003218736 | A1 | 20030922 | AU 2003-218736 | 20030311 |
| EP 1485353 | A1 | 20041215 | EP 2003-711980 | 20030311 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| BR 2003008081 | A | 20041221 | BR 2003-8081 | 20030311 |
| CN 1639125 | A | 20050713 | CN 2003-805675 | 20030311 |
| CN 1642551 | A | 20050720 | CN 2003-805833 | 20030311 |
| NZ 534834 | A | 20050729 | NZ 2003-534834 | 20030311 |
| JP 2005526067 | T | 20050902 | JP 2003-574621 | 20030311 |
| CN 101007803 | A | 20070801 | CN 2007-10005212 | 20030311 |
| IN 2004DN02533 | A | 20070413 | IN 2004-DN2533 | 20040831 |
| US 20050107384 | A1 | 20050519 | US 2004-506998 | 20040908 |
| ZA 2004007237 | A | 20050928 | ZA 2004-7237 | 20040909 |
| ZA 2004007235 | A | 20051004 | ZA 2004-7235 | 20040909 |
| ZA 2004007232 | A | 20051006 | ZA 2004-7232 | 20040909 |
| ZA 2004007233 | A | 20051006 | ZA 2004-7233 | 20040909 |
| ZA 2004007234 | A | 20051006 | ZA 2004-7234 | 20040909 |
| ZA 2004007236 | A | 20051006 | ZA 2004-7236 | 20040909 |
| MX 2004PA08806 | A | 20041126 | MX 2004-PA8806 | 20040910 |
| NO 2004004194 | A | 20041001 | NO 2004-4194 | 20041001 |
| PRIORITY APPLN. INFO.: | | | US 2002-363799P | P 20020313 |
| | | | WO 2002-EP14833 | A 20021223 |
| | | | CN 2003-805921 | A3 20030311 |

OTHER SOURCE(S):
GI

MARPAT 139:261309



AB The title compds. [I; n = 0-3; t = 0-4; Q, X, Y = N, C; Z = N, CH; R1 = CONR7R8, NHCOR9, CO(alkanediyl)SR9, etc. (wherein R7, R8 = H, OH, alkyl, etc.; R9 = H, alkyl, alkylcarbonyl, etc.); R2 = H, halo, OH, etc.; L = a bond, alkanediyl, alkanediyoxy, NH, CO, NHCO; each R3 = H and one H atom can be replaced by aryl; R4 = H, OH, NH2, etc.; A = (un)substituted Ph, cyclohexyl, pyridyl, etc.], having histone deacetylase inhibiting enzymic activity, were prepared and formulated. E.g., a multi-step synthesis of II which showed pIC50 of 5.121 against HDAC, was given.

IT 603985-83-7P 603985-87-1P 603985-89-3P
603985-91-7P 603985-95-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of piperazino(piperidino or diazepino) substituted 2-pyrimidinecarbohydroxamic acids and N-hydroxybenzamides as new inhibitors of histone deacetylase)

RN 603985-83-7 CAPLUS

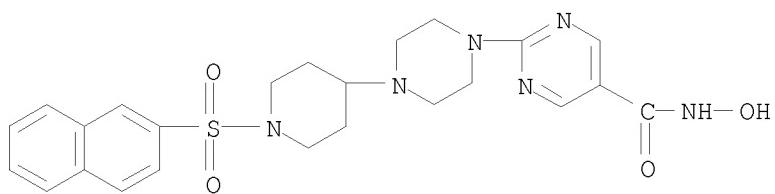
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(2-naphthalenylsulfonyl)-4-piperidinyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (10:9) (CA INDEX NAME)

CM 1

CRN 603985-82-6

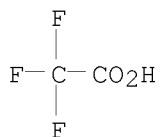
CMF C24 H28 N6 O4 S

10/513699



CM 2

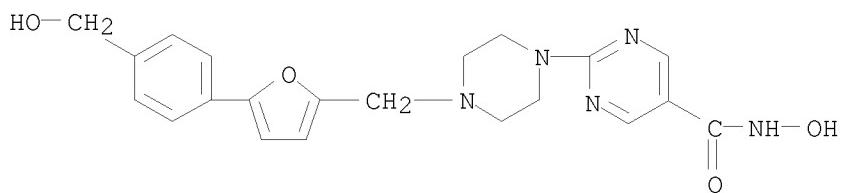
CRN 76-05-1
CMF C2 H F3 O2



RN 603985-87-1 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(5-[4-(hydroxymethyl)phenyl]-2-furanyl)methyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

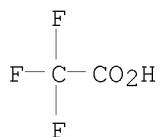
CM 1

CRN 603985-86-0
CMF C21 H23 N5 O4



CM 2

CRN 76-05-1
CMF C2 H F3 O2



10/513699

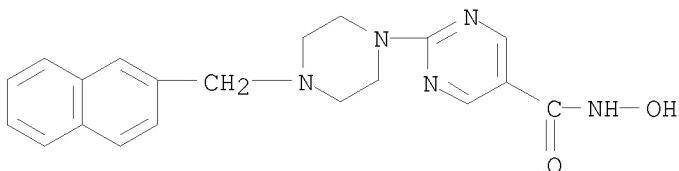
RN 603985-89-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-88-2

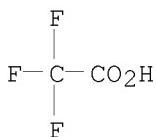
CMF C20 H21 N5 O2



CM 2

CRN 76-05-1

CMF C2 H F3 O2



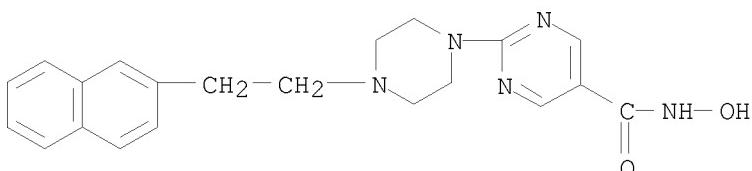
RN 603985-91-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-90-6

CMF C21 H23 N5 O2

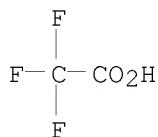


CM 2

CRN 76-05-1

CMF C2 H F3 O2

10/513699



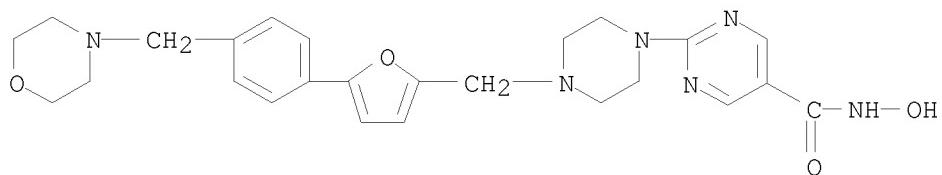
RN 603985-95-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl-, 2,2,2-trifluoroacetate (1:2) (CA INDEX NAME)

CM 1

CRN 603985-94-0

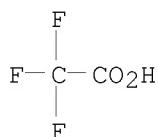
CMF C25 H30 N6 O4



CM 2

CRN 76-05-1

CMF C2 H F3 O2



REFERENCE COUNT:

3

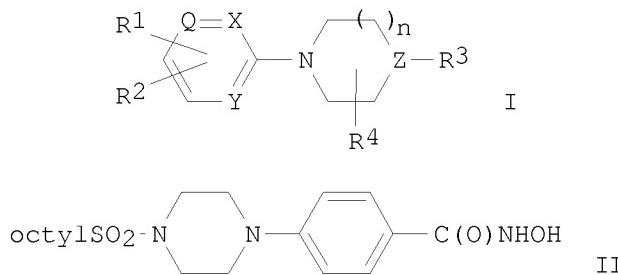
THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN
 ACCESSION NUMBER: 2003:737586 CAPLUS
 DOCUMENT NUMBER: 139:261308
 TITLE: Preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases
 INVENTOR(S): Van Emelen, Kristof; Verdonck, Marc Gustaaf Celine; Van Brandt, Sven Franciscus Anna; Angibaud, Patrick Rene; Meerpoel, Lieven; Dyatkin, Alexey Borisovich Janssen Pharmaceutica N.V., Belg.
 PATENT ASSIGNEE(S):
 SOURCE: PCT Int. Appl., 52 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 8
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|-------------|
| WO 2003075929 | A1 | 20030918 | WO 2003-EP2515 | 20030311 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2476065 | A1 | 20030918 | CA 2003-2476065 | 20030311 |
| AU 2003218737 | A1 | 20030922 | AU 2003-218737 | 20030311 |
| AU 2003218737 | B2 | 20080410 | | |
| EP 1485099 | A1 | 20041215 | EP 2003-711981 | 20030311 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| BR 2003007624 | A | 20050111 | BR 2003-7624 | 20030311 |
| CN 1639125 | A | 20050713 | CN 2003-805675 | 20030311 |
| CN 1642551 | A | 20050720 | CN 2003-805833 | 20030311 |
| JP 2005525379 | T | 20050825 | JP 2003-574203 | 20030311 |
| NZ 534832 | A | 20050930 | NZ 2003-534832 | 20030311 |
| CN 101007803 | A | 20070801 | CN 2007-10005212 | 20030311 |
| IN 2004DN02537 | A | 20070112 | IN 2004-DN2537 | 20040831 |
| ZA 2004007237 | A | 20050928 | ZA 2004-7237 | 20040909 |
| ZA 2004007235 | A | 20051004 | ZA 2004-7235 | 20040909 |
| ZA 2004007232 | A | 20051006 | ZA 2004-7232 | 20040909 |
| ZA 2004007233 | A | 20051006 | ZA 2004-7233 | 20040909 |
| ZA 2004007234 | A | 20051006 | ZA 2004-7234 | 20040909 |
| ZA 2004007236 | A | 20051006 | ZA 2004-7236 | 20040909 |
| MX 2004PA08797 | A | 20041126 | MX 2004-PA8797 | 20040910 |
| US 20050096468 | A1 | 20050505 | US 2004-507785 | 20040913 |
| NO 2004004113 | A | 20040928 | NO 2004-4113 | 20040928 |
| PRIORITY APPLN. INFO.: | | | US 2002-363799P | P 20020313 |
| | | | WO 2002-EP14833 | A 20021223 |
| | | | CN 2003-805921 | A3 20030311 |
| | | | WO 2003-EP2515 | W 20030311 |

OTHER SOURCE(S): MARPAT 139:261308

GI



AB This invention comprises aryl and heteroaryl hydroxamic acids (shown as I; variables defined below; e.g. II) having histone deacetylase inhibiting enzymic activity; their preparation, compns. containing them and their use as a medicine. Compds. I show excellent in-vitro histone deacetylase inhibiting enzymic activity, have advantageous properties with regard to cellular activity and specific properties with regard to inhibition of cell cycle progression at both G1 and G2 checkpoints (p21 induction capacity), and show good metabolic stability and high bioavailability and more particular show oral bioavailability. They can also be used for detection and identification of histone deacetylase. General synthetic procedures and characterization data for twenty-seven I are included; also, preps. of 12 intermediates are included. For example, a 59 % yield of 2-[4-(dimethylaminosulfonyl)piperazin-1-yl]pyrimidine-5-carbohydroxamic acid was obtained by removing the O-tetrahydropyranyl group of its ester using trifluoroacetic acid; the ester was prepared in 61 % yield from N'-(ethylcarbonimidoyl)-N,N-dimethyl-1,3-propanediamine monohydrochloride, sodium 2-[4-(dimethylaminosulfonyl)piperazin-1-yl]pyrimidine-5-carboxylate, O-(tetrahydro-2H-pyran-2-yl)hydroxylamine, and 1-hydroxy-1H-benzotriazole in CH₂Cl₂/THF. The sodium salt was obtained by base hydrolysis of the Et ester; the ester was prepared in 73 % yield from Et 2-(piperazin-1-yl)pyrimidine-5-carboxylate and dimethylsulfamoyl chloride; Et 2-(piperazin-1-yl)pyrimidine-5-carboxylate was obtained in <96 % yield from Et 2-(4-benzylpiperazin-1-yl)pyrimidine-5-carboxylate by hydrogenation using Pd/C; the benzyl derivative was obtained from 1-(phenylmethyl)piperazine, (135 mL) was added gradually to a solution of potassium carbonate (0.18 mol) and 2-(methylsulfonyl)-5-pyrimidinecarboxylic acid Et ester, K₂CO₃ in MeCN. For I: n is 0-3; Q, X and Y are N or C; Z is N or CH; R1 is -C(O)NR5R6, -N(H)C(O)R7, -C(O)-C1-6alkanediylSR7, -NR8C(O)N(OH)R7, -NR8C(O)C1-6alkanediylSR7, -NR8C(O)C:N(OH)R7 or another Zn-chelating-group; R2 is H, halo, hydroxy, amino, nitro, C1-6alkyl, C1-6alkyloxy, trifluoromethyl, di(C1-6-alkyl)amino, hydroxyamino or naphthalenylsulfonylpnazinyl. R3 is H, C1-6-alkyl, arylC2-6alkenediyl, furanylcarbonyl, naphthalenylcarbonyl, -C(O)phenylR9, C1-6alkylaminocarbonyl, aminosulfonyl, arylaminosulfonyl, aminosulfonylamino, di(C1-6-alkyl)aminosulfonylamino, arylaminosulfonylamino, aminosulfonylaminoc1-6-alkyl, di(C1-6-alkyl)aminosulfonylaminoc1-6-alkyl, arylaminosulfonylaminoc1-6alkyl, di(C1-6-alkyl)aminoC1-6alkyl, C11-12-alkylsulfonyl, di(C1-6-alkyl)aminosulfonyl, trihaloC1-6-alkylsulfonyl, di(aryl)C1-6alkylcarbonyl, thiophenylC1-6alkylcarbonyl, pyridinylcarbonyl or arylC1-6alkylcarbonyl. R4 is H, hydroxy, amino, hydroxyC1-6alkyl, C1-6alkyl, C1-6alkyloxy,

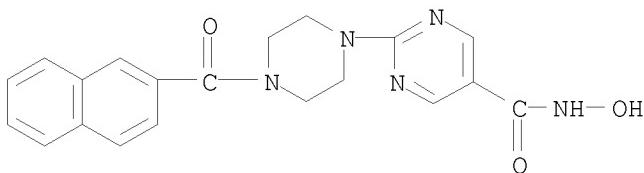
arylC1-6alkyl, aminocarbonyl, hydroxycarbonyl, aminoC1-6-alkyl, aminocarbonylC1-6-alkyl, hydroxycarbonylC1-6-alkyl, hydroxyaminocarbonyl, C1-6-alkyloxycarbonyl, C1-6-alkylaminoC1-6-alkyl or di(C1-6-alkyl)aminoC1-6-alkyl; when R3 and R4 are present on the same C atom, R3 and R4 together may form -C(O)-NH-CH₂-NR10- wherein R10 is H or aryl; when R3 and R4 are present on adjacent C atoms, R3 and R4 together may form :CH-CH:CH-CH: ; addnl. details are given in the claims.

IT 603991-96-4P
 RL: ARG (Analytical reagent use); PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate and reagent for detection/identification of histone deacetylase; preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases)

RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



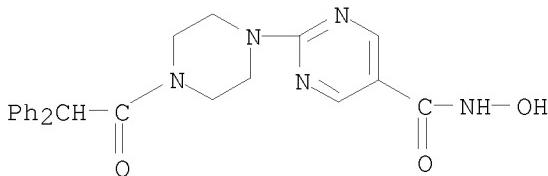
IT 603991-95-3P 603992-24-1P 603992-25-2P
 603992-26-3P 603992-27-4P 603992-28-5P

RL: ARG (Analytical reagent use); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate and reagent for detection/identification of histone deacetylase; preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases)

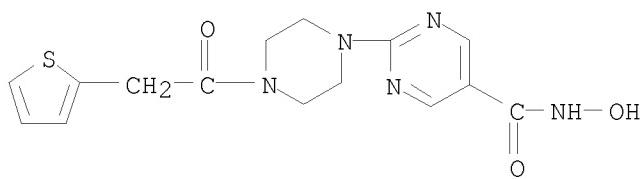
RN 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



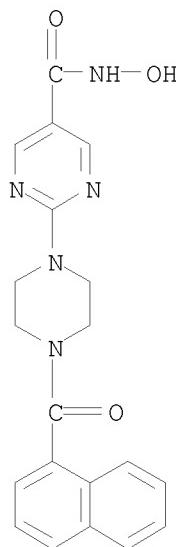
RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)



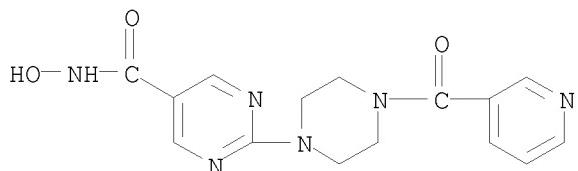
RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



RN 603992-26-3 CAPLUS

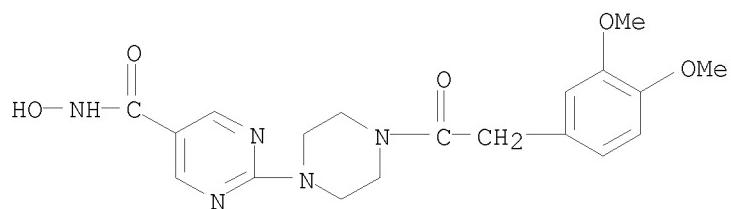
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



RN 603992-27-4 CAPLUS

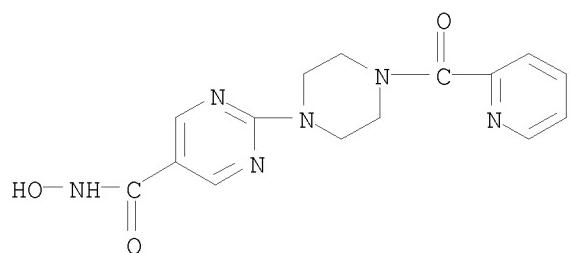
CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

10/513699



RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



REFERENCE COUNT:

6

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/513699

=> file erg
'ERG' IS NOT A VALID FILE NAME
SESSION CONTINUES IN FILE 'CAPLUS'
Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files
that are available. If you have requested multiple files, you can
specify a corrected file name or you can enter "IGNORE" to continue
accessing the remaining file names entered.

=> file reg

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|--|------------------|---------------|
| FULL ESTIMATED COST | 71.33 | 671.99 |
| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
| CA SUBSCRIBER PRICE | -10.40 | -19.20 |

FILE 'REGISTRY' ENTERED AT 16:08:09 ON 15 SEP 2008
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2008 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 14 SEP 2008 HIGHEST RN 1049627-95-3
DICTIONARY FILE UPDATES: 14 SEP 2008 HIGHEST RN 1049627-95-3

New CAS Information Use Policies, enter HELP USAGETERMS for details.

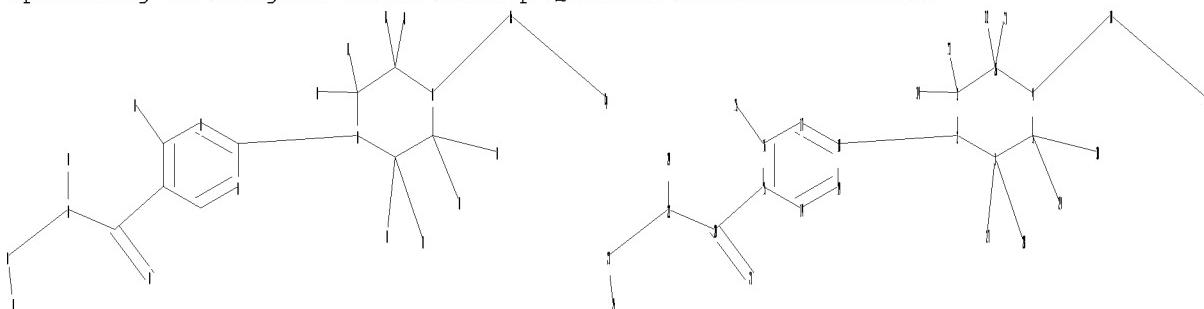
TSCA INFORMATION NOW CURRENT THROUGH July 5, 2008.

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

<http://www.cas.org/support/stnexp/stndoc/properties.html>

=>
Uploading C:\Program Files\Stnexp\Queries\10506998five.str



10/513699

chain nodes :
10 11 20 21 22 23 24 25 27 28 29 30 31 32 33 34 35
ring nodes :
1 2 3 4 5 14 15 16 17 18 19 26
chain bonds :
1-27 1-28 2-18 3-33 3-34 4-10 5-29 5-30 10-11 15-20 16-35 20-21 20-22
22-23 22-24 23-25 26-31 26-32
ring bonds :
1-2 1-5 2-3 3-26 4-5 4-26 14-15 14-19 15-16 16-17 17-18 18-19
exact/norm bonds :
1-2 1-5 2-3 2-18 3-26 4-10 4-5 4-26 10-11 20-21 20-22 22-23
exact bonds :
1-27 1-28 3-33 3-34 5-29 5-30 15-20 16-35 22-24 23-25 26-31 26-32
normalized bonds :
14-15 14-19 15-16 16-17 17-18 18-19
isolated ring systems :
containing 1 :

G1:C,N

G2:Ak,NH2,NO2

G3:O

G4

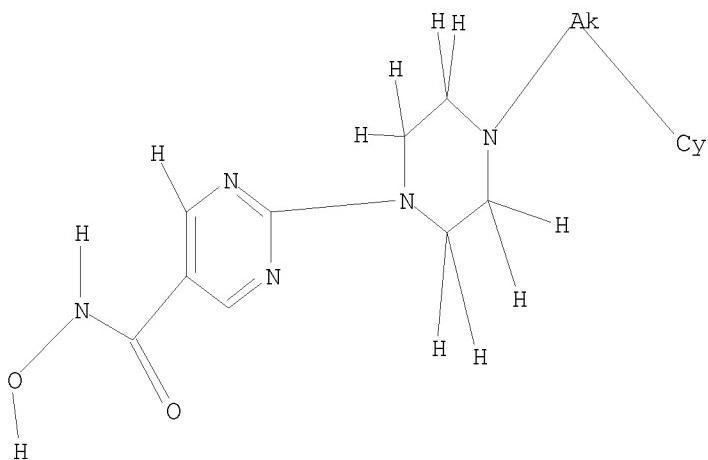
G5:C,N,Zn,H

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 10:CLASS 11:Atom 14:Atom 15:Atom
16:Atom 17:Atom 18:Atom 19:Atom 20:CLASS 21:CLASS 22:CLASS 23:CLASS
24:CLASS 25:CLASS 26:Atom 27:CLASS 28:CLASS 29:CLASS 30:CLASS 31:CLASS
32:CLASS 33:CLASS 34:CLASS 35:CLASS

L12 STRUCTURE UPLOADED

=> d l12
L12 HAS NO ANSWERS
L12 STR

10/513699



G1 C,N

G2 Ak,NH₂,NO₂

G3 O

G4

G5 C,N,Zn,H

Structure attributes must be viewed using STN Express query preparation.

=> s 112 full
FULL SEARCH INITIATED 16:08:56 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 1679 TO ITERATE

100.0% PROCESSED 1679 ITERATIONS 89 ANSWERS
SEARCH TIME: 00.00.01

L13 89 SEA SSS FUL L12

=> file caplus
COST IN U.S. DOLLARS SINCE FILE TOTAL
ENTRY SESSION
FULL ESTIMATED COST 178.82 850.81

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) SINCE FILE TOTAL
ENTRY SESSION
CA SUBSCRIBER PRICE 0.00 -19.20

FILE 'CAPLUS' ENTERED AT 16:09:04 ON 15 SEP 2008
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2008 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December

10/513699

26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 15 Sep 2008 VOL 149 ISS 12
FILE LAST UPDATED: 14 Sep 2008 (20080914/ED)

Caplus now includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2008.

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

<http://www.cas.org/legal/infopolICY.html>

=> s 113 full
L14 9 L13

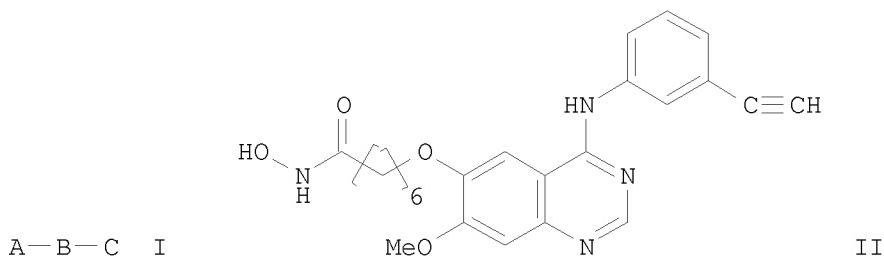
=> d ibib abs hitstr tot

L14 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2008:353001 CAPLUS
DOCUMENT NUMBER: 148:355828
TITLE: Multi-functional small molecules as anti-proliferative agents and their preparation
INVENTOR(S): Cai, Xiong; Qian, Changcheng; Gould, Stephen; Zhai, Haixiao
PATENT ASSIGNEE(S): Curis, Inc., USA
SOURCE: PCT Int. Appl., 494pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|----------|-----------------|------------|
| WO 2008033747 | A2 | 20080320 | WO 2007-US77971 | 20070910 |
| WO 2008033747 | A9 | 20080724 | | |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG,
KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL,
PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | |
| RW: | AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW,
GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA | | | |
| US 20080221132 | A1 | 20080911 | US 2007-852458 | 20070910 |
| PRIORITY APPLN. INFO.: | | | US 2006-843590P | P 20060911 |
| | | | US 2007-895889P | P 20070320 |

OTHER SOURCE(S): MARPAT 148:355828

GI

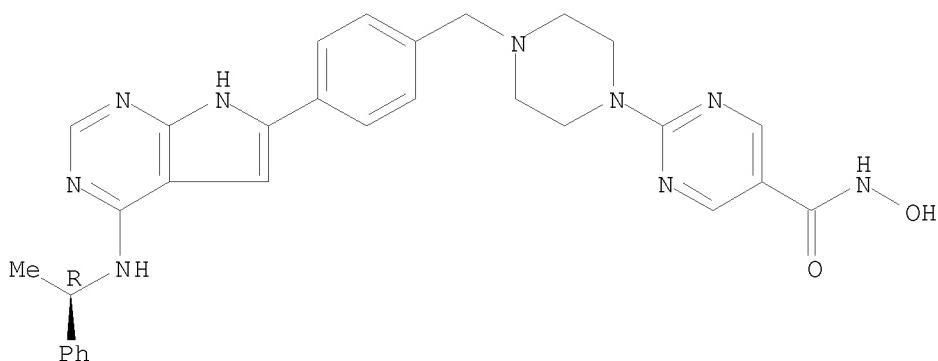


AB The invention relates to the compns., methods, and applications of an approach to selective inhibition of several cellular or mol. targets with a single small mol. More specifically, the present invention relates to multi-functional small mols. of formula I wherein one functionality is capable of inhibiting histone deacetylases (HDAC) and the other functionality is capable of inhibiting a different cellular or mol. pathway involved in aberrant cell proliferation, differentiation or

survival. Compds. of formula I wherein A is a pharmacophore of an anticancer agent capable of inhibiting at least one cellular or mol. pathway involved in the aberrant cell proliferation, differentiation or survival; B is a linker; C is a zinc-binding moiety; and their geometrical isomers, enantiomers, diastereoisomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, are claimed. Example compound II was prepared by a multistep procedure (procedure given). All the invention compds. were evaluated for their antiproliferative activity (some data given).

- IT 1011716-90-7P
 RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRPH (Prophetic); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prophetic starting material; preparation of multi-functional small mols. as antiproliferative agents)
- RN 1011716-90-7 CAPLUS
- CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[4-[(1R)-1-phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN
 ACCESSION NUMBER: 2008:351928 CAPLUS
 DOCUMENT NUMBER: 148:355814
 TITLE: Preparation of (aralkylamino)(phenyl)pyrrolo[2,3-d]pyrimidine derivatives for use as protein tyrosine kinase (PTK) inhibitors
 INVENTOR(S): Cai, Xiong; Qian, Changgeng; Gould, Stephen
 PATENT ASSIGNEE(S): Curis, Inc., USA
 SOURCE: PCT Int. Appl., 123pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2008033745 | A2 | 20080320 | WO 2007-US77968 | 20070910 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| US 20080161320 | A1 | 20080703 | US 2007-852440 | 20070910 |
| PRIORITY APPLN. INFO.: | | | US 2006-843646P | P 20060911 |
| | | | US 2007-895894P | P 20070320 |

OTHER SOURCE(S): MARPAT 148:355814
 GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Fused bicyclic pyrimidine derivs. I and II [Ar = aryl, substituted arylheteroaryl or heteroaryl; Q = absent or (un)substituted alkyl; X = O, S, NH, or aralkylamino; Z = O, S, NR1; Y = N or CR2; B = linker; D = C(O)NH2, NHC(S)CH3, CHC(O)NHacyl, etc.; R1 = H or (un)substituted alkyl; R2 = H, halo, (un)substituted aliphatic, aryl or heteroaryl], and their pharmaceutically acceptable salts, are prepared and disclosed as protein tyrosine kinase (PTK) inhibitors. Thus, e.g., III was prepared by N-alkylation of 1,4-dioxa-8-azaspiro[4.5]decane with 6-(4-(chloromethyl)phenyl)-N-((R)-1-phenylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (preparation given) and deprotection followed by condensation with 6-aminohexanoic acid Me ester and amidation with hydroxylamine. Select I were evaluated in EGFR assays, e.g., III demonstrated an IC50 value of ≤ 0.1 (μ M).

IT 1011716-90-7P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

10/513699

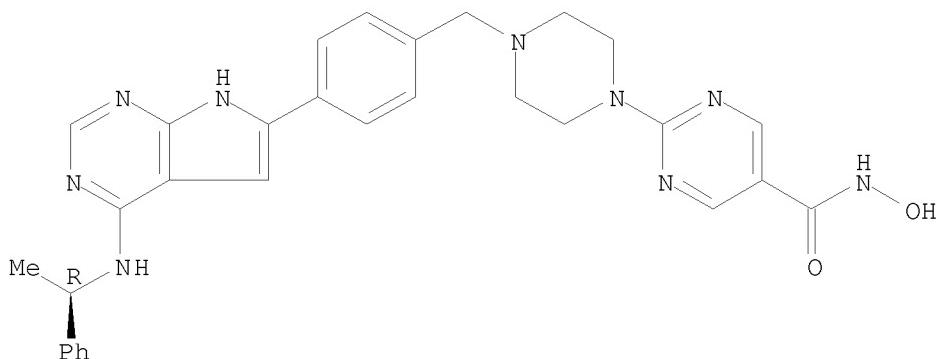
(Uses)

(preparation of (aralkylamino)(phenyl)pyrrolopyrimidine derivs. for use as protein tyrosine kinase (PTK) inhibitors)

RN 1011716-90-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[4-[[4-[(1R)-1-phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

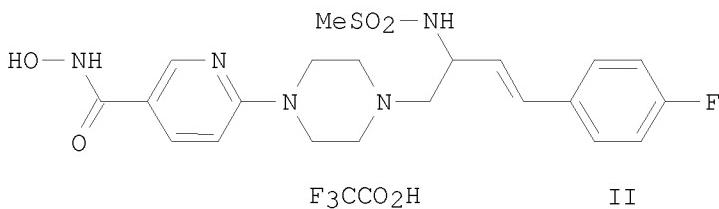
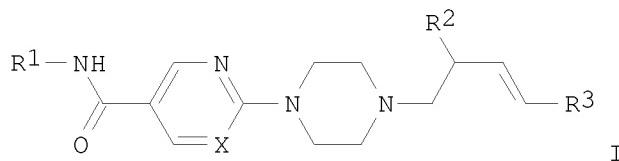
Absolute stereochemistry.



L14 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN
 ACCESSION NUMBER: 2007:816930 CAPLUS
 DOCUMENT NUMBER: 147:211903
 TITLE: Preparation of pyrimidine derivatives as histone deacetylase inhibitors
 INVENTOR(S): Marconnet-Decrane, Laurence Francoise Bernadette; Gaurrand, Sandrine Francoise Dominique; Angibaud, Patrick Rene
 PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.
 SOURCE: PCT Int. Appl., 62pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2007082874 | A1 | 20070726 | WO 2007-EP50371 | 20070116 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN,
KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK,
MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO,
RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT,
TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM | | | | |
| CA 2630717 | A1 | 20070726 | CA 2007-2630717 | 20070116 |
| PRIORITY APPLN. INFO.: | | | EP 2006-100570 | A 20060119 |
| | | | WO 2007-EP50371 | W 20070116 |

OTHER SOURCE(S): MARPAT 147:211903
 GI



AB The title compds. with general formula I [wherein R1 = OH or substituted phenyl; X = N or CH; R2 = amino, alkylamino, alkoxy, OH, etc.; R3 = (un)substituted Ph, naphthalene, or heterocycle] or N-oxide forms, pharmaceutically acceptable salts, or stereoisomeric forms thereof were prepared as histone deacetylase (HDAC) inhibitors for the treatment of proliferative diseases. For example, compound II was prepared in a multi-step synthesis. In vitro assay for inhibition of HDAC was performed to measure the inhibition of HDAC enzymic activity, and colorimetric assay was performed to determine cellular activity on A2780 tumor cells. II showed HDAC inhibitory and anti-proliferative activities in the above two assays with pIC₅₀ values of 7.0 and 5.3, resp. Formulations containing I as active ingredients were also reported.

IT 944738-91-4P 944738-94-7P 944738-97-0P

944739-00-8P 944739-08-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrimidine derivs. as histone deacetylase inhibitors)

RN 944738-91-4 CAPLUS

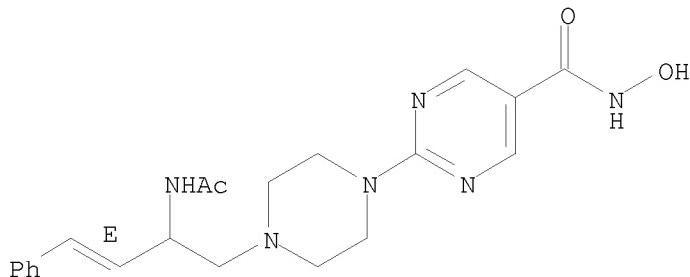
CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(acetylamino)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-90-3

CMF C21 H26 N6 O3

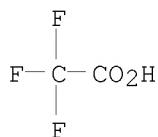
Double bond geometry as shown.



CM 2

CRN 76-05-1

CMF C2 H F3 O2



10/513699

RN 944738-94-7 CAPLUS

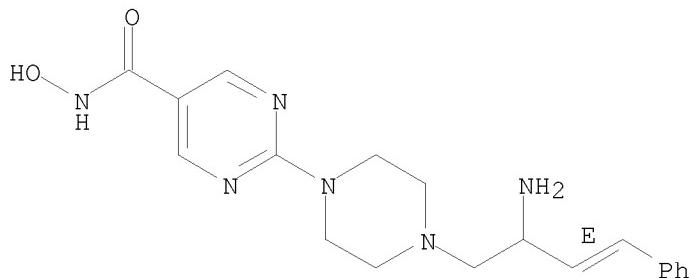
CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-amino-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-93-6

CMF C19 H24 N6 O2

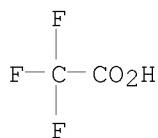
Double bond geometry as shown.



CM 2

CRN 76-05-1

CMF C2 H F3 O2



RN 944738-97-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(2,5-dioxo-1-pyrrolidinyl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

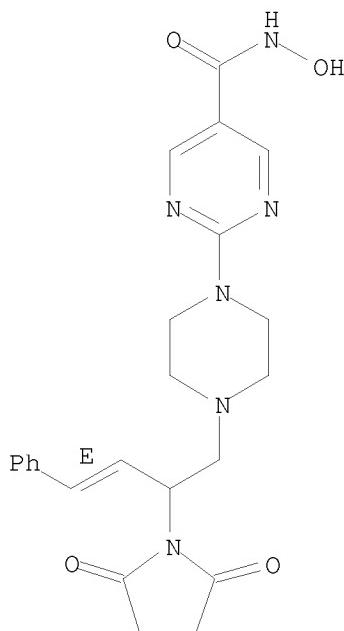
CM 1

CRN 944738-96-9

CMF C23 H26 N6 O4

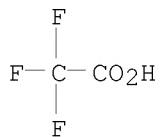
Double bond geometry as shown.

10/513699



CM 2

CRN 76-05-1
CMF C2 H F3 O2



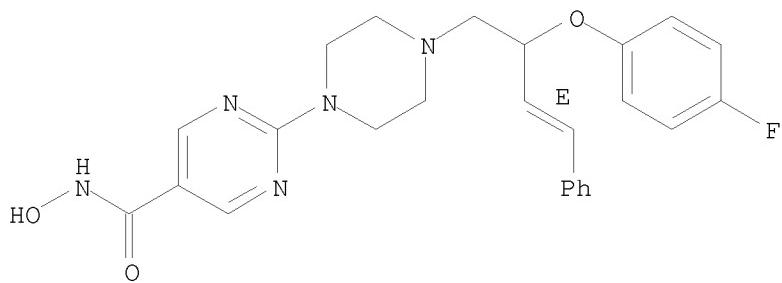
RN 944739-00-8 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(4-fluorophenoxy)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-99-2
CMF C25 H26 F N5 O3

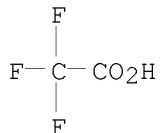
Double bond geometry as shown.

10/513699



CM 2

CRN 76-05-1
CMF C2 H F3 O2

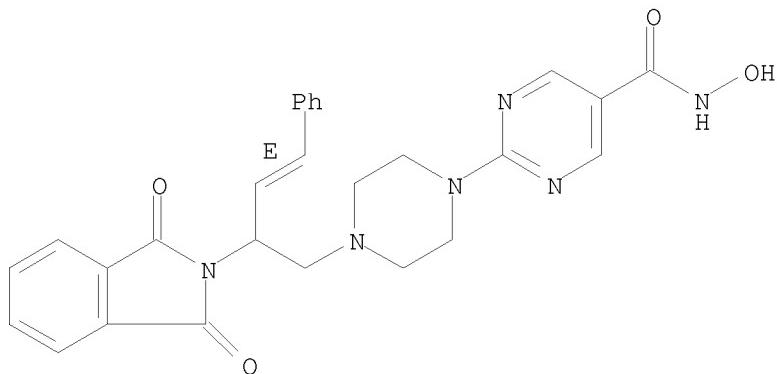


RN 944739-08-6 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944739-07-5
CMF C27 H26 N6 O4

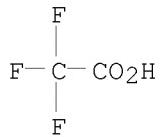
Double bond geometry as shown.



CM 2

10/513699

CRN 76-05-1
CMF C2 H F3 O2



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/513699

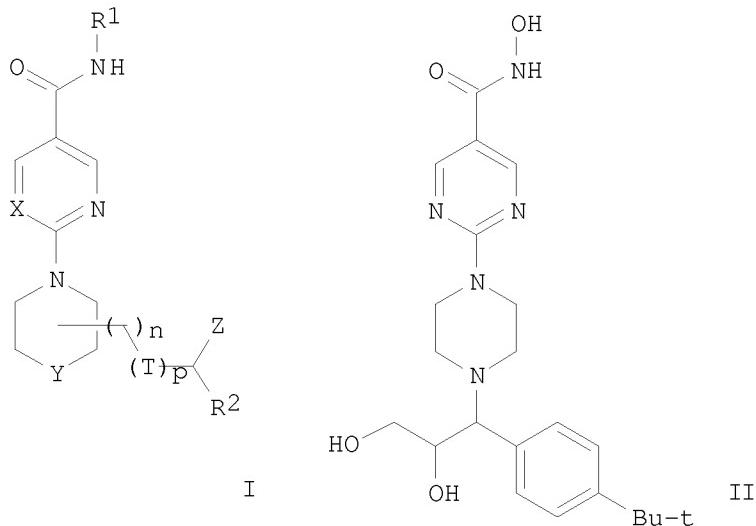
L14 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:816806 CAPLUS
DOCUMENT NUMBER: 147:211902
TITLE: Preparation of pyrimidine derivatives as histone deacetylase inhibitors
INVENTOR(S): Angibaud, Patrick Rene; Van Brandt, Sven Franciscus Anna; Marconnet-Decrane, Laurence Francoise Bernadette; Roux, Bruno
PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.
SOURCE: PCT Int. Appl., 63pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2007082880 | A1 | 20070726 | WO 2007-EP50379 | 20070116 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |

PRIORITY APPLN. INFO.: EP 2006-100571 A 20060119

OTHER SOURCE(S): MARPAT 147:211902

GI



IT 944712-03-2P 944712-05-4P 944712-07-6P
944712-09-8P 944712-10-1P 944712-12-3P

944712-14-5P 944712-16-7P 944712-18-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrimidine derivs. as histone deacetylase inhibitors)

RN 944712-03-2 CAPLUS

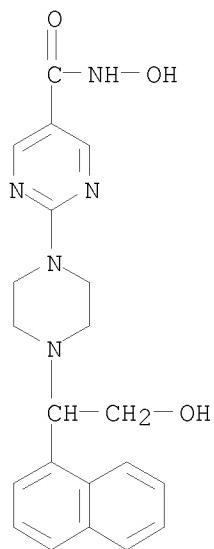
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-(1-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-02-1

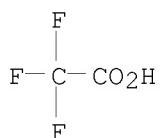
CMF C21 H23 N5 O3

10/513699



CM 2

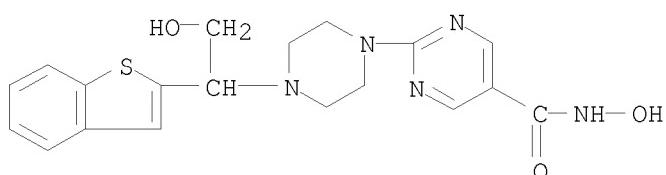
CRN 76-05-1
CMF C₂ H F₃ O₂



RN 944712-05-4 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-(1-benzo[b]thien-2-yl-2-hydroxyethyl)-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

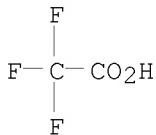
CRN 944712-04-3
CMF C₁₉ H₂₁ N₅ O₃ S



CM 2

10/513699

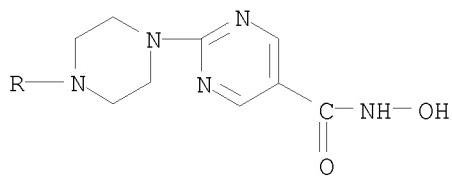
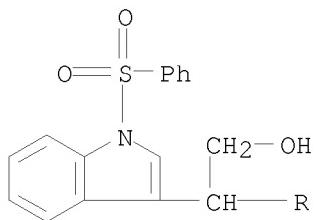
CRN 76-05-1
CMF C2 H F3 O2



RN 944712-07-6 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-[1-(phenylsulfonyl)-1H-indol-3-yl]ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

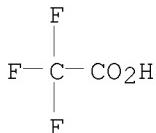
CM 1

CRN 944712-06-5
CMF C25 H26 N6 O5 S



CM 2

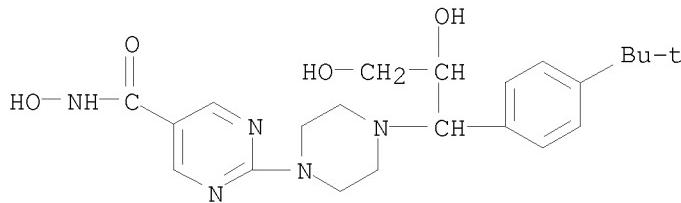
CRN 76-05-1
CMF C2 H F3 O2



RN 944712-09-8 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[1-[4-(1,1-dimethylethyl)phenyl]-2,3-

10/513699

dihydroxypropyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



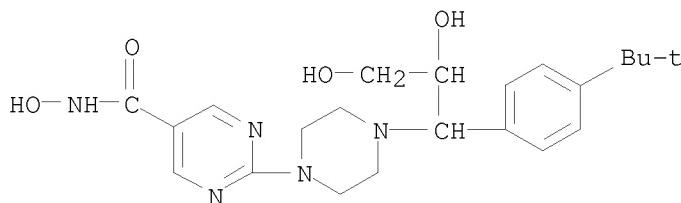
RN 944712-10-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1)
(CA INDEX NAME)

CM 1

CRN 944712-09-8

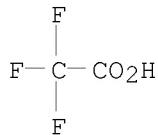
CMF C22 H31 N5 O4



CM 2

CRN 76-05-1

CMF C2 H F3 O2



RN 944712-12-3 CAPLUS

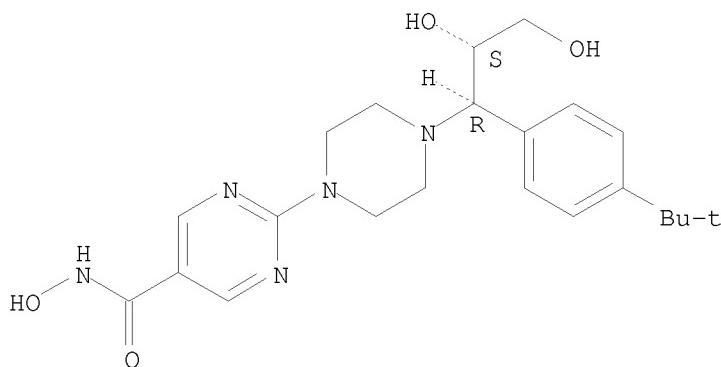
CN 5-Pyrimidinecarboxamide, 2-[4-[1R,2S)-1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?)
(CA INDEX NAME)

CM 1

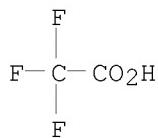
CRN 944712-11-2

CMF C22 H31 N5 O4

Absolute stereochemistry.

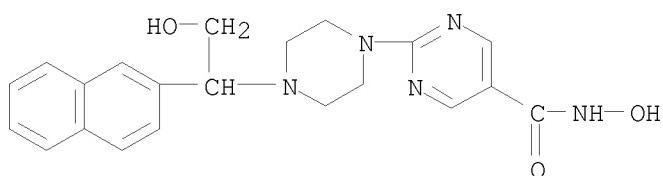


CM 2

CRN 76-05-1
CMF C2 H F3 O2

RN 944712-14-5 CAPLUS
 CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-(2-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

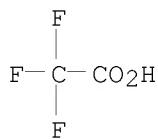
CM 1

CRN 944712-13-4
CMF C21 H23 N5 O3

CM 2

CRN 76-05-1
CMF C2 H F3 O2

10/513699



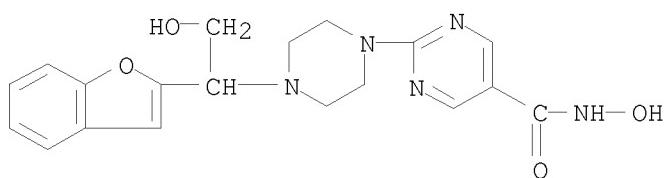
RN 944712-16-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-(2-benzofuranyl)-2-hydroxyethyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-15-6

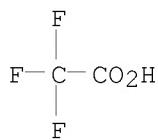
CMF C19 H21 N5 O4



CM 2

CRN 76-05-1

CMF C2 H F3 O2



RN 944712-18-9 CAPLUS

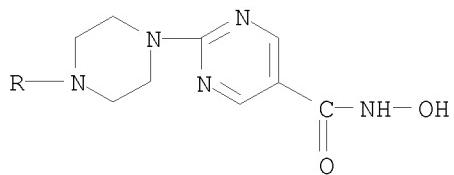
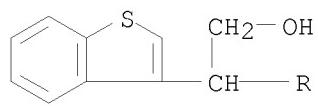
CN 5-Pyrimidinecarboxamide, 2-[4-(1-benzo[b]thien-3-yl-2-hydroxyethyl)-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-17-8

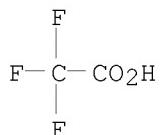
CMF C19 H21 N5 O3 S

10/513699



CM 2

CRN 76-05-1
CMF C2 H F3 O2

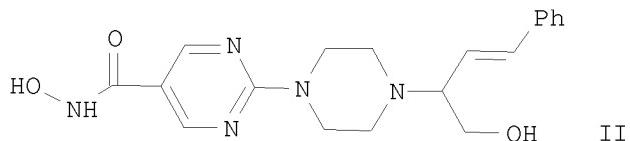
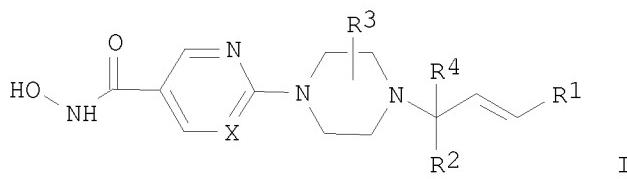


REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN
 ACCESSION NUMBER: 2006:101446 CAPLUS
 DOCUMENT NUMBER: 144:192266
 TITLE: Preparation of substituted propenyl piperazine derivatives as novel inhibitors of histone deacetylase
 INVENTOR(S): Van Brandt, Sven Franciscus Anna; Van Emelen, Kristof; Angibaud, Patrick Rene; Marconnet-Decrane, Laurence Francoise Bernadette; Arts, Janine
 PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.
 SOURCE: PCT Int. Appl., 67 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|------------|
| WO 2006010749 | A2 | 20060202 | WO 2005-EP53611 | 20050725 |
| WO 2006010749 | A3 | 20060608 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ,
LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA,
NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK,
SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU,
ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM | | | | |
| AU 2005266311 | A1 | 20060202 | AU 2005-266311 | 20050725 |
| CA 2572971 | A1 | 20060202 | CA 2005-2572971 | 20050725 |
| EP 1776358 | A2 | 20070425 | EP 2005-777776 | 20050725 |
| R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL,
BA, HR, MK, YU | | | | |
| CN 1993356 | A | 20070704 | CN 2005-80025487 | 20050725 |
| JP 2008508234 | T | 20080321 | JP 2007-523072 | 20050725 |
| BR 2005013891 | A | 20080520 | BR 2005-13891 | 20050725 |
| KR 2007043978 | A | 20070426 | KR 2007-701641 | 20070123 |
| US 20070135424 | A1 | 20070614 | US 2007-626215 | 20070123 |
| IN 2007DN00658 | A | 20070803 | IN 2007-DN658 | 20070124 |
| MX 200701119 | A | 20070315 | MX 2007-1119 | 20070126 |
| NO 2007001117 | A | 20070227 | NO 2007-1117 | 20070227 |
| PRIORITY APPLN. INFO.: | | | EP 2004-77171 | A 20040728 |
| | | | US 2004-592357P | P 20040729 |
| | | | WO 2005-EP53611 | W 20050725 |

OTHER SOURCE(S): CASREACT 144:192266; MARPAT 144:192266
 GI



AB Substituted propenyl piperazine derivs. I, wherein X is independently N or CH; R1 is Ph, naphthalenyl or heterocyclyl; wherein each of said Ph or naphthalenyl is optionally substituted with one or two substituents each independently selected from halo, alkyl, alkyloxy, poly-halo-alkyl, aryl, hydroxy, cyano, amino, alkylcarbonylamino, alkylsulfonylamino, hydroxycarbonyl, alkyloxycarbonyl, hydroxyalkyl, alkyloxymethyl, aminomethyl, alkylaminomethyl, alkylcarbonylaminomethyl, alkylsulfonylaminomethyl, aminosulfonyl, alkylaminosulfonyl or heterocyclyl; R2 is hydrogen, -CH₂R₅, trifluoromethyl, -C(O)-R₆, or -CH-NR₇R₈; wherein each R₅ is independently hydrogen, hydroxy, alkyloxy, alkyloxyalkyloxy, alkylcarbonyloxy, piperazinyl, N-methylpiperazinyl, morpholinyl, thiomorpholinyl, imidazolyl or triazolyl; each R₆ is independently hydroxy, alkyloxy, amino or mono- or di(alkyl)amino, cycloalkylamino, hydroxyalkylamino, piperazinyl, N-methylpiperazinyl, morpholinyl or thiomorpholinyl; each R₇ and R₈ are independently hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, or mono- or di(alkyl)aminosulfonyl; R₃ is hydrogen, hydroxymethyl, aminomethyl or mono- or di(alkyl)aminomethyl; R₄ is hydrogen or alkyl; were prepared and having histone deacetylase inhibiting enzymic activity and to inhibit proliferative conditions, such as cancer and psoriasis. Thus, propenyl piperazine derivative II was prepared and tested in vitro and in nude mice as inhibitor of histone deacetylase and was better than R306465 after oral administration. P21 enzyme linked immunosorbent assay has been applied to determine the p21 protein expression level in human A2780 ovarian carcinoma cells. In vitro assay for inhibition of histone deacetylase is reported. P21 induction was measured as the consequence of DNA damage or as the consequence of histone deacetylase inhibition. Antiproliferative activity of title compds. was determined on A2780 cells (neg. log value of the IC₅₀, pIC₅₀ = 7.9-8.2).

IT 875138-85-5P 875138-87-7P 875138-88-8P
 875138-89-9P 875138-90-2P 875138-91-3P
 875138-93-5P 875138-94-6P 875138-98-0P
 875139-00-7P 875139-02-9P 875139-04-1P
 875139-06-3P 875139-07-4P 875139-09-6P
 875139-11-0P 875139-13-2P 875139-14-3P
 875139-15-4P 875139-17-6P 875139-19-8P
 875139-20-1P 875139-21-2P 875139-23-4P
 875139-24-5P 875139-25-6P 875139-26-7P
 875139-27-8P 875139-28-9P 875139-29-0P
 875139-30-3P 875139-31-4P 875139-69-8P

10/513699

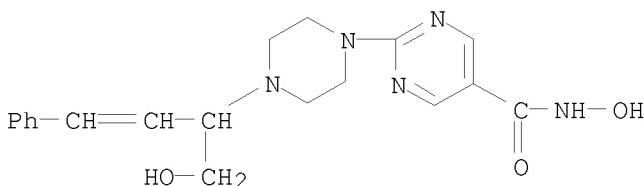
875139-70-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of substituted propenyl piperazine derivs. as novel inhibitors of histone deacetylase)

RN 875138-85-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)



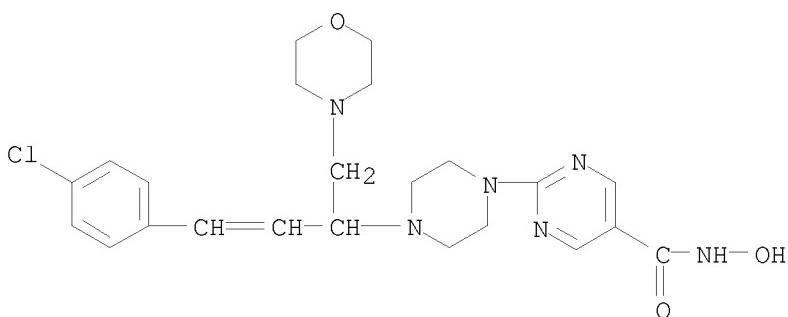
RN 875138-87-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-chlorophenyl)-1-(4-morpholinylmethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-86-6

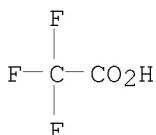
CMF C23 H29 Cl N6 O3



CM 2

CRN 76-05-1

CMF C2 H F3 O2

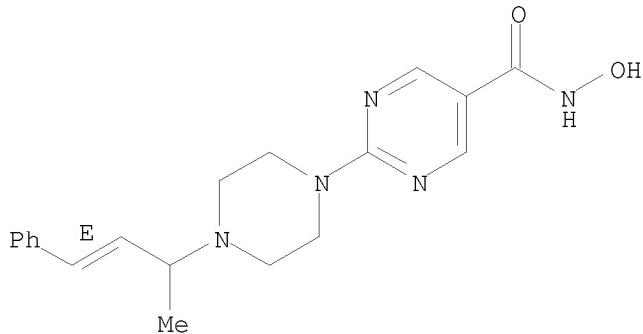


10/513699

RN 875138-88-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-methyl-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Double bond geometry as shown.



RN 875138-89-9 CAPLUS

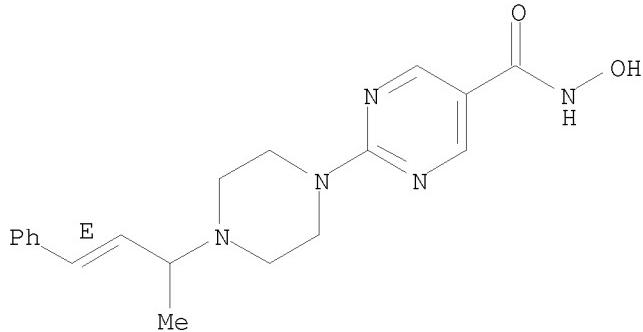
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-methyl-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-88-8

CMF C19 H23 N5 O2

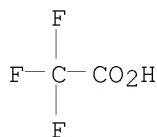
Double bond geometry as shown.



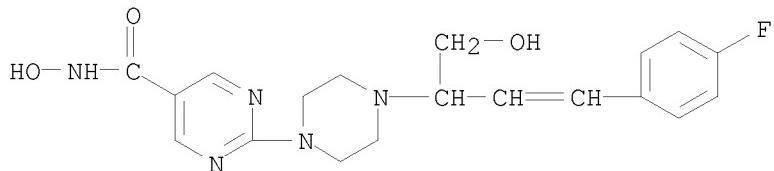
CM 2

CRN 76-05-1

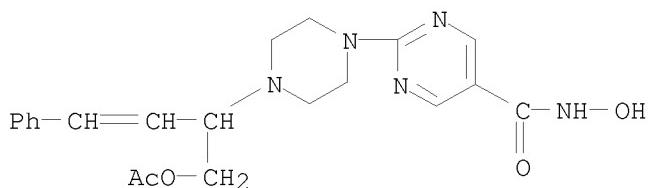
CMF C2 H F3 O2



RN 875138-90-2 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



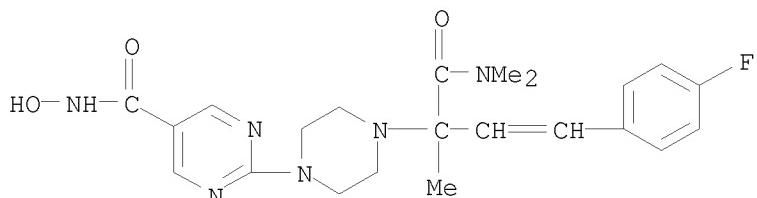
RN 875138-91-3 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(acetyloxy)methyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



RN 875138-93-5 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(dimethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

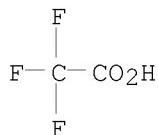
CRN 875138-92-4
 CMF C22 H27 F N6 O3



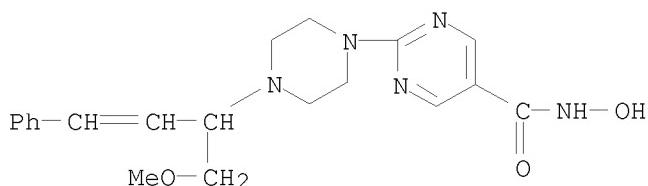
CM 2

10/513699

CRN 76-05-1
CMF C2 H F3 O2



RN 875138-94-6 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(methoxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

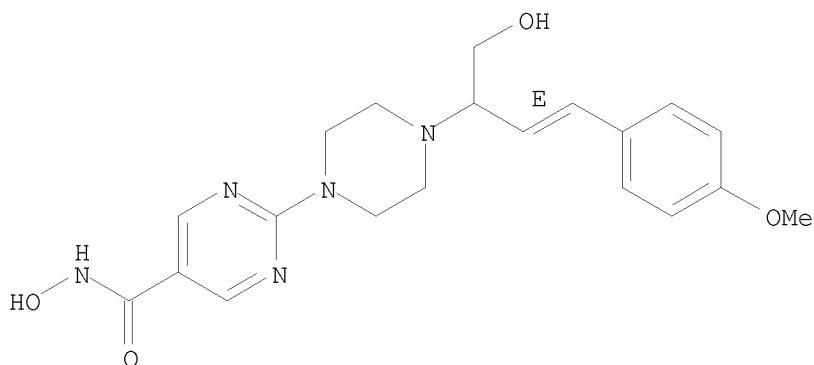


RN 875138-98-0 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-(hydroxymethyl)-3-(4-methoxyphenyl)-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-97-9
CMF C20 H25 N5 O4

Double bond geometry as shown.

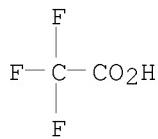


CM 2

CRN 76-05-1

10/513699

CMF C2 H F3 O2



RN 875139-00-7 CAPLUS

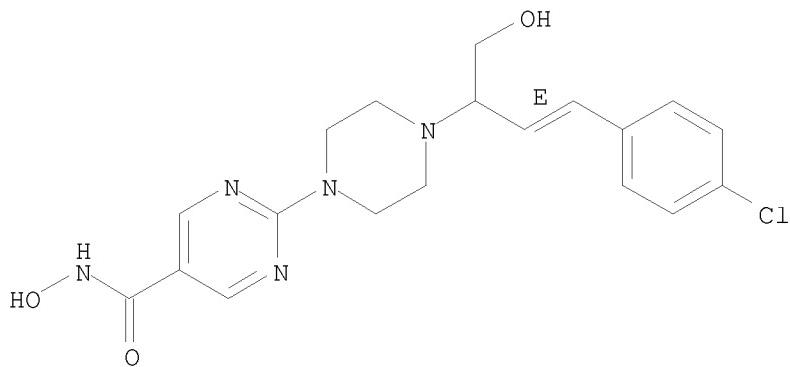
CN 5-Pyrimidinecarboxamide, 2-[4-[(2E)-3-(4-chlorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-99-1

CMF C19 H22 Cl N5 O3

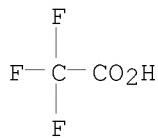
Double bond geometry as shown.



CM 2

CRN 76-05-1

CMF C2 H F3 O2



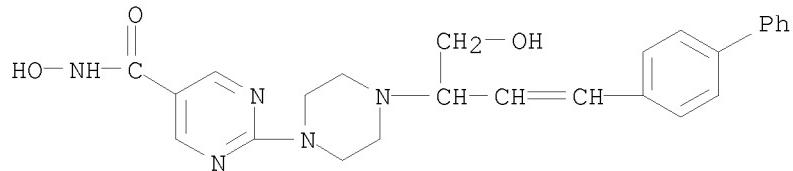
RN 875139-02-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-[1,1'-biphenyl]-4-yl-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

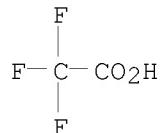
10/513699

CRN 875139-01-8
CMF C25 H27 N5 O3



CM 2

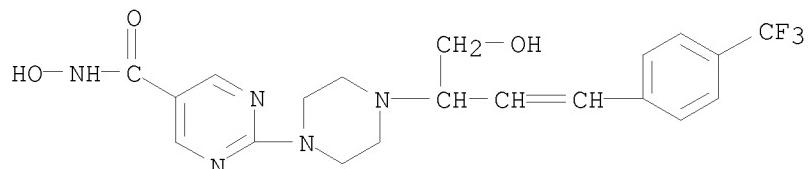
CRN 76-05-1
CMF C2 H F3 O2



RN 875139-04-1 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(hydroxymethyl)-3-[4-(trifluoromethyl)phenyl]-2-propen-1-yl]piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

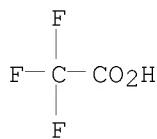
CRN 875139-03-0
CMF C20 H22 F3 N5 O3



CM 2

CRN 76-05-1
CMF C2 H F3 O2

10/513699



RN 875139-06-3 CAPLUS

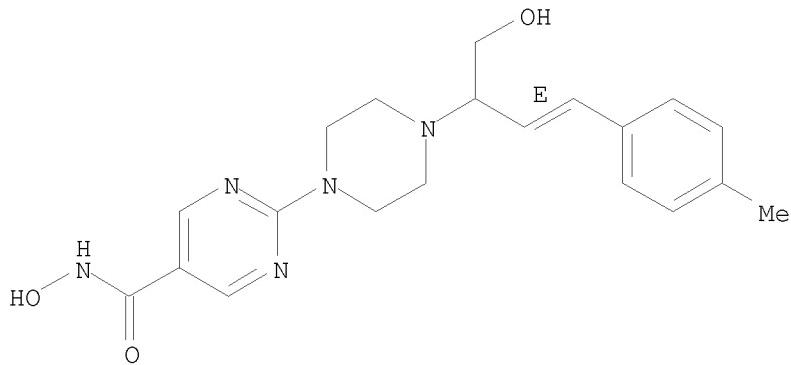
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-(hydroxymethyl)-3-(4-methylphenyl)-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-05-2

CMF C20 H25 N5 O3

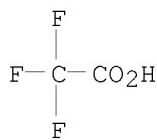
Double bond geometry as shown.



CM 2

CRN 76-05-1

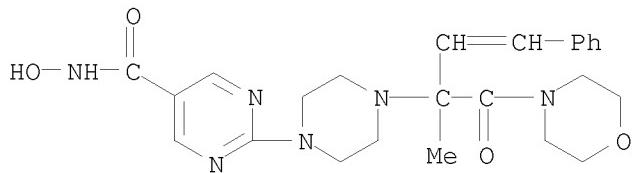
CMF C2 H F3 O2



RN 875139-07-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(1-methyl-1-(4-morpholinylcarbonyl)-3-phenyl-2-propen-1-yl)-1-piperazinyl]- (CA INDEX NAME)

10/513699



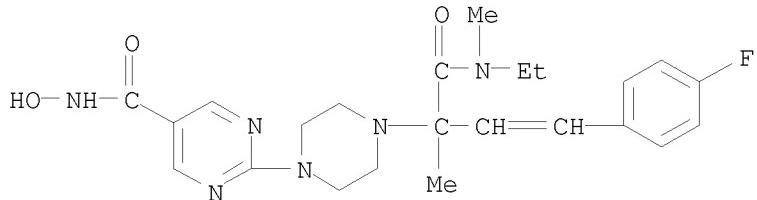
RN 875139-09-6 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(ethylmethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-08-5

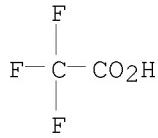
CMF C23 H29 F N6 O3



CM 2

CRN 76-05-1

CMF C2 H F3 O2



RN 875139-11-0 CAPLUS

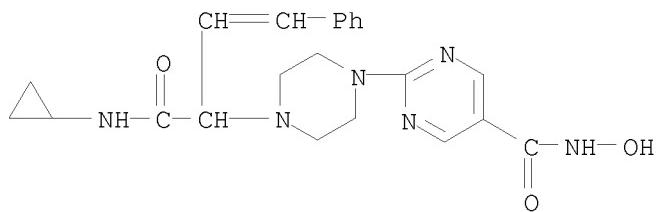
CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(cyclopropylamino)carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-10-9

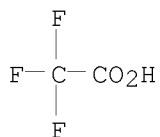
CMF C22 H26 N6 O3

10/513699



CM 2

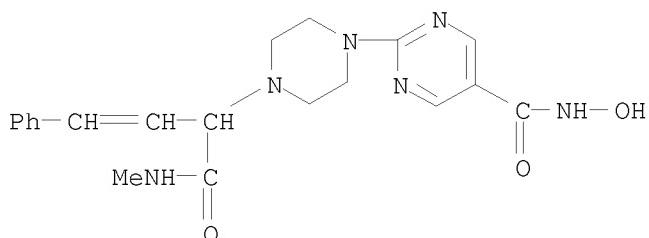
CRN 76-05-1
CMF C2 H F3 O2



RN 875139-13-2 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-[(methylamino)carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

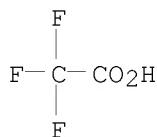
CRN 875139-12-1
CMF C20 H24 N6 O3



CM 2

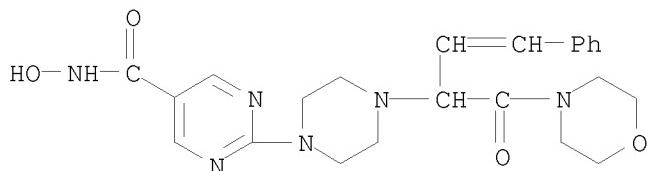
CRN 76-05-1
CMF C2 H F3 O2

10/513699



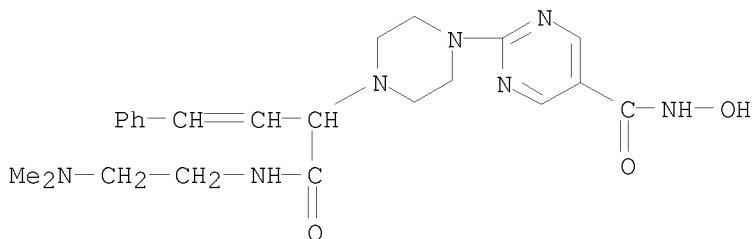
RN 875139-14-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(4-morpholinylcarbonyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)



RN 875139-15-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[[(2-(dimethylamino)ethyl]amino]carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



RN 875139-17-6 CAPLUS

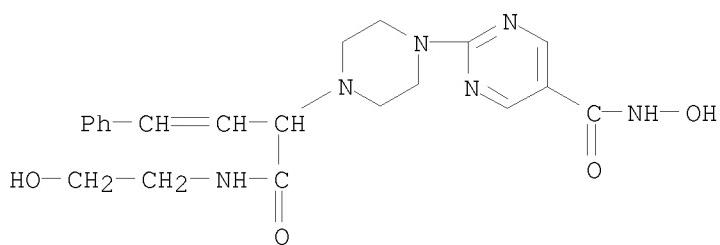
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-[[(2-hydroxyethyl)amino]carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-16-5

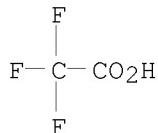
CMF C21 H26 N6 O4

10/513699



CM 2

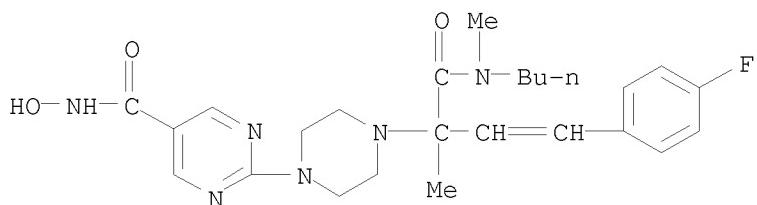
CRN 76-05-1
CMF C2 H F3 O2



RN 875139-19-8 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[(butylmethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

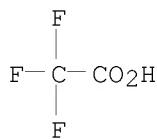
CRN 875139-18-7
CMF C25 H33 F N6 O3



CM 2

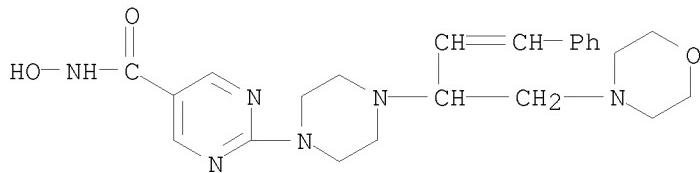
CRN 76-05-1
CMF C2 H F3 O2

10/513699



RN 875139-20-1 CAPLUS

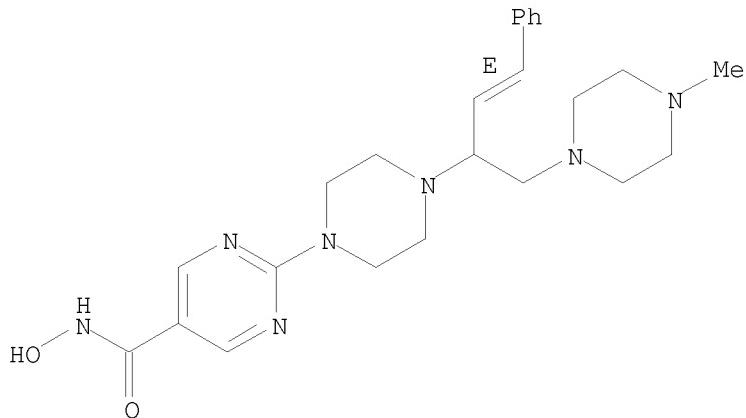
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(4-morpholinylmethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)



RN 875139-21-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[((2E)-1-[(4-methyl-1-piperazinyl)methyl]-3-phenyl-2-propen-1-yl)-1-piperazinyl]- (CA INDEX NAME)

Double bond geometry as shown.



RN 875139-23-4 CAPLUS

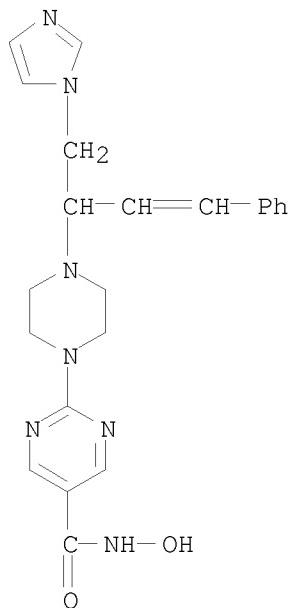
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(1H-imidazol-1-ylmethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-22-3

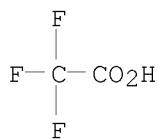
CMF C22 H25 N7 O2

10/513699

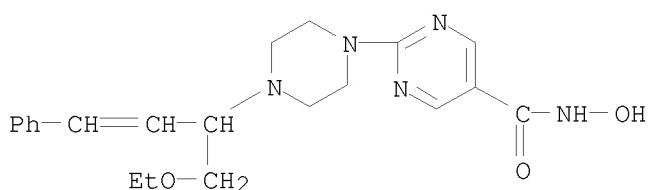


CM 2

CRN 76-05-1
CMF C2 H F3 O2



RN 875139-24-5 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[1-(ethoxymethyl)-3-phenyl-2-propenyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

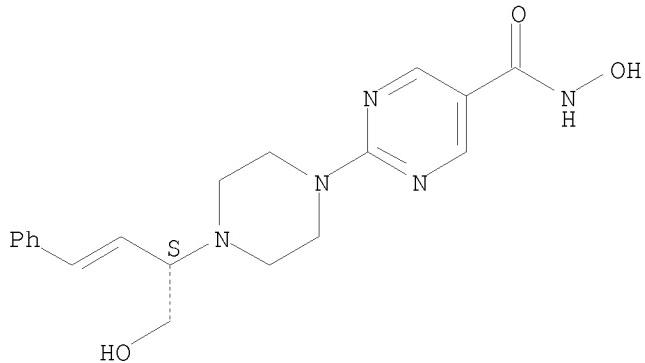


RN 875139-25-6 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(1S)-1-(hydroxymethyl)-3-phenyl-2-propenyl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

10/513699

Double bond geometry unknown.

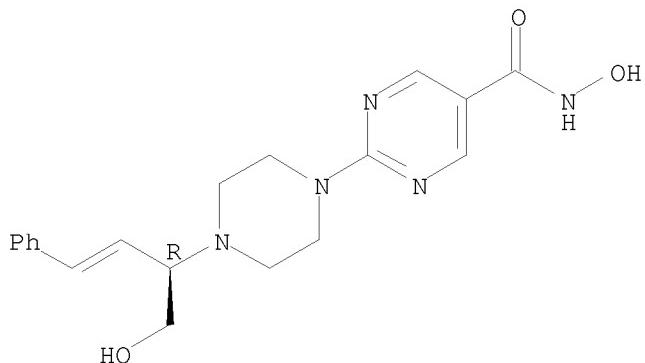


RN 875139-26-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(1R)-1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

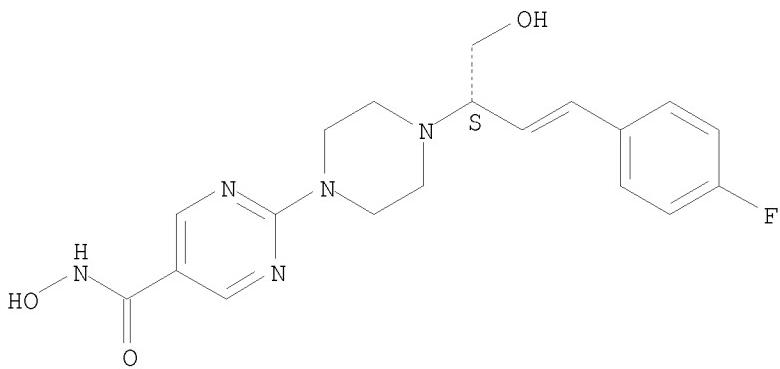


RN 875139-27-8 CAPLUS

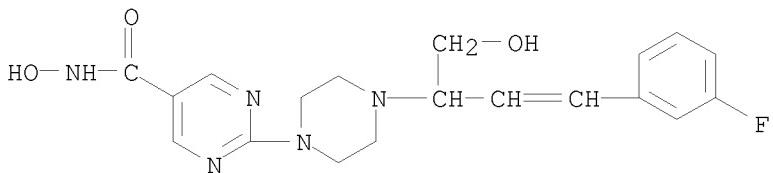
CN 5-Pyrimidinecarboxamide, 2-[4-[(1S)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.

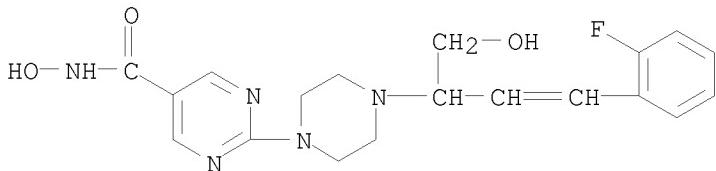
Double bond geometry unknown.



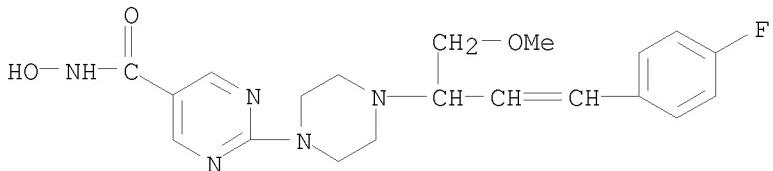
RN 875139-28-9 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[3-(3-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



RN 875139-29-0 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[3-(2-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



RN 875139-30-3 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-fluorophenyl)-1-(methoxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

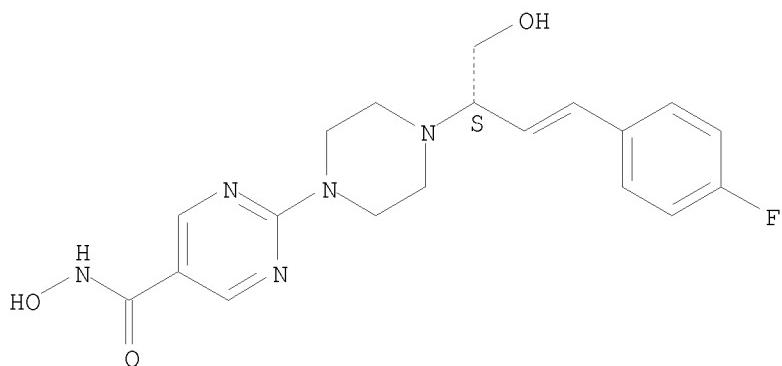


RN 875139-31-4 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-fluorophenyl)-1-(hydroxymethyl)-2-

10/513699

propen-1-yl]-1-piperazinyl]-N-hydroxy-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

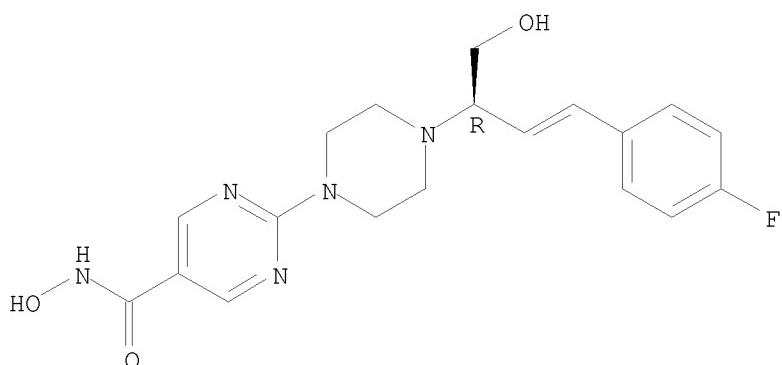


● HCl

RN 875139-69-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

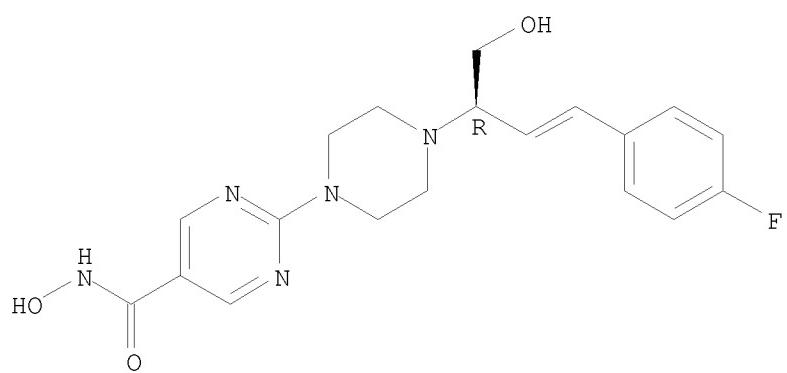


RN 875139-70-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

10/513699

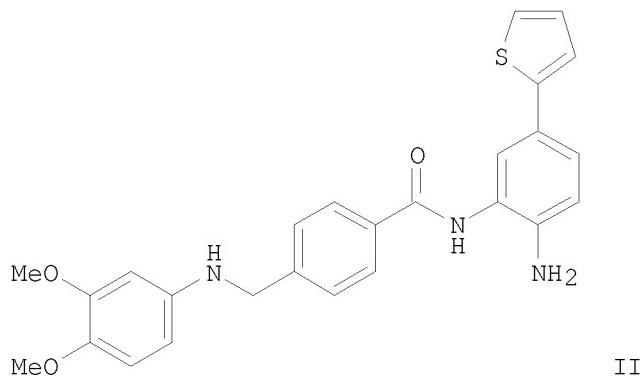
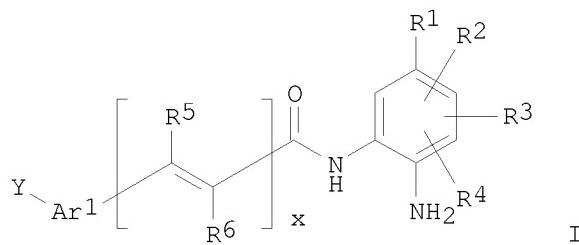


● HCl

10/513699

L14 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:300395 CAPLUS
DOCUMENT NUMBER: 142:355054
TITLE: Preparation of amide derivatives as inhibitors of histone deacetylase
INVENTOR(S): Moradei, Oscar; Paquin, Isabelle; Leit, Silvana;
Frechette, Sylvie; Vaisburg, Arkadii; Besterman,
Jeffrey M.; Tessier, Pierre; Mallais, Tammy C.
PATENT ASSIGNEE(S): Methylgene, Inc., Can.
SOURCE: PCT Int. Appl., 559 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|--|----------|------------------|-------------|
| WO 2005030705 | A1 | 20050407 | WO 2004-US31591 | 20040924 |
| WO 2005030705 | A9 | 20060420 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG | | | | |
| AU 2004276337 | A1 | 20050407 | AU 2004-276337 | 20040924 |
| CA 2539117 | A1 | 20050407 | CA 2004-2539117 | 20040924 |
| EP 1663953 | A1 | 20060607 | EP 2004-789074 | 20040924 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR | | | | |
| CN 1882529 | A | 20061220 | CN 2004-80034571 | 20040924 |
| JP 2007506785 | T | 20070322 | JP 2006-528279 | 20040924 |
| US 20080132459 | A1 | 20080605 | US 2006-574088 | 20060323 |
| JP 2008094847 | A | 20080424 | JP 2007-281356 | 20071030 |
| PRIORITY APPLN. INFO.: | | | US 2003-505884P | P 20030924 |
| | | | US 2003-532973P | P 20031229 |
| | | | US 2004-561082P | P 20040409 |
| | | | JP 2006-528279 | A3 20040924 |
| | | | WO 2004-US31591 | W 20040924 |
| OTHER SOURCE(S): GI | CASREACT 142:355054; MARPAT 142:355054 | | | |



AB Title compds. I [Ar1 = (un)saturated-, (un)substituted-mono or fused poly-cyclic hydrocarbyl optionally containing 1-4 heteroatoms per ring; R1 = (un)substituted-mono-, -bi-, -tri-cyclic-aryl or -heteroaryl; R2, R3, and R4 independently = H, halo, amino, etc.; R5 and R6 independently = H, alkyl, aryl, etc.; x = 0-1; Y = any pharmaceutically acceptable chemical moiety consisting of 1 to 50 atoms with provisions] and their pharmaceutically acceptable salts, are prepared and disclosed as inhibitors of histone deacetylase. Thus, e.g., II was prepared by Suzuki coupling of 2-bromo-2-nitro-phenylamine (preparation given) with 2-thiopheneboronic acid followed by carbonylation with 4-[3,4-dimethoxy-(phenylamino)-methyl]benzoic acid (preparation given) and subsequent reduction. The inhibitory

capability of I towards antiproliferative activity of histone deacetylase enzyme was evaluated using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay and it revealed that certain compds. of the invention had MTT IC₅₀ values in the range of below 1 up to 20 μM. I as histone deacetylase inhibitors should prove useful in the treatment of diseases such as, but not limited to, cell proliferative disease, protozoal disease, and fungal disease.

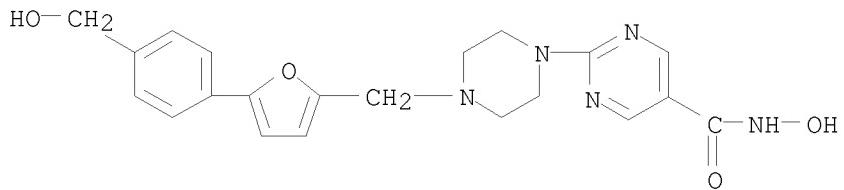
IT 603985-86-0P 603985-88-2P 603985-90-6P
603985-94-0P 603991-95-3P 603991-96-4P
603992-24-1P 603992-25-2P 603992-26-3P
603992-27-4P 603992-28-5P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

RN (preparation of amide derivs. as inhibitors of histone deacetylase)
603985-86-0 CAPLUS

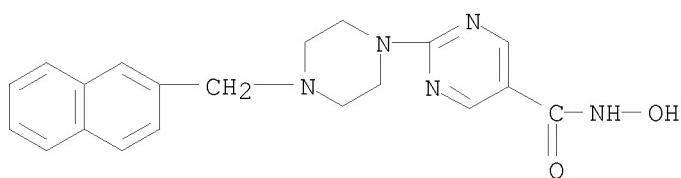
10/513699

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl- (CA INDEX NAME)



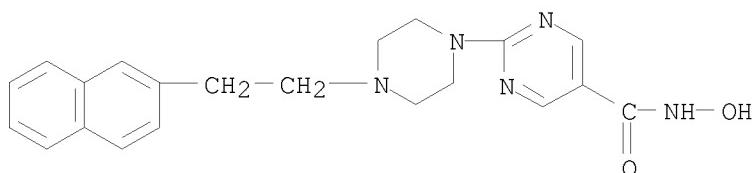
RN 603985-88-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl- (CA INDEX NAME)



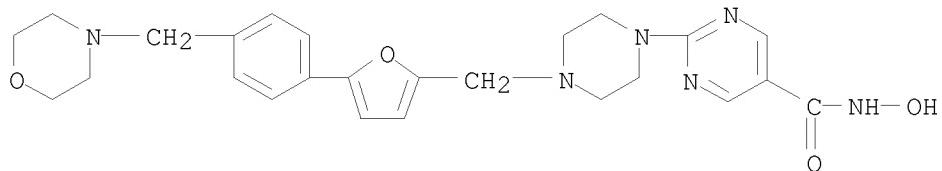
RN 603985-90-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl- (CA INDEX NAME)



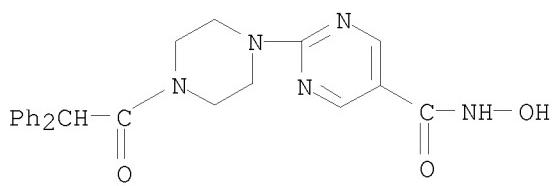
RN 603985-94-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl- (CA INDEX NAME)



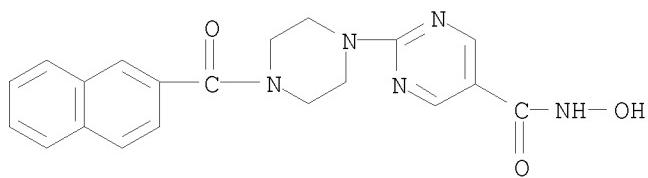
RN 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



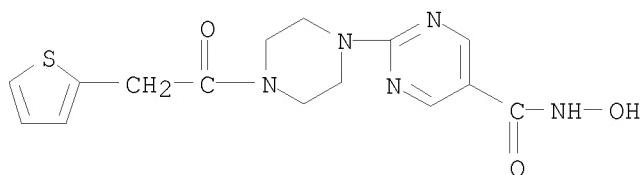
RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



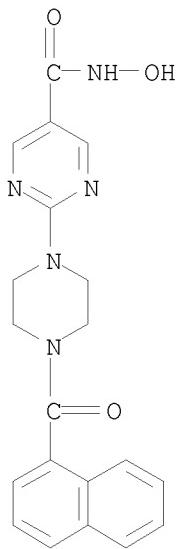
RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)

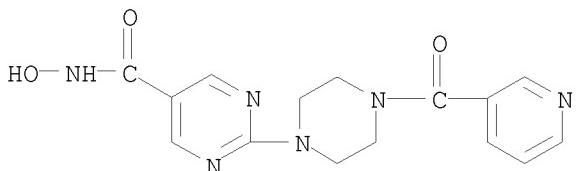


RN 603992-25-2 CAPLUS

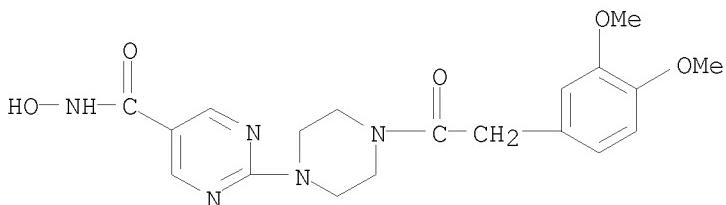
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



RN 603992-26-3 CAPLUS
 CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

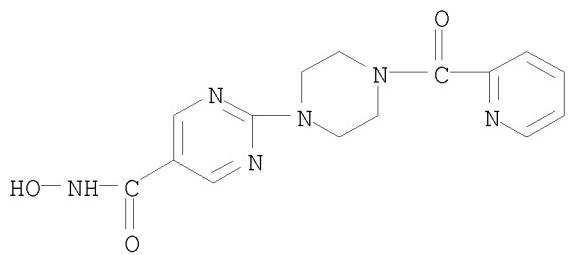


RN 603992-27-4 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



RN 603992-28-5 CAPLUS
 CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

10/513699



REFERENCE COUNT:

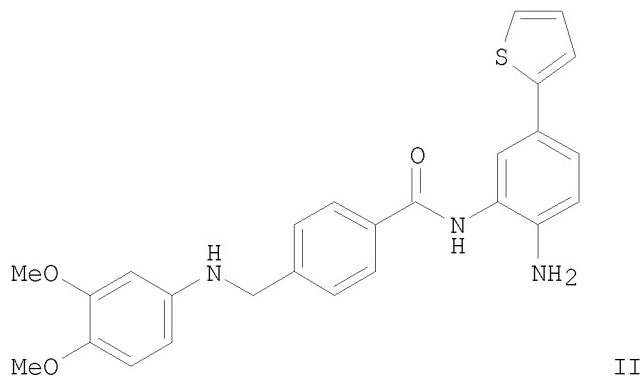
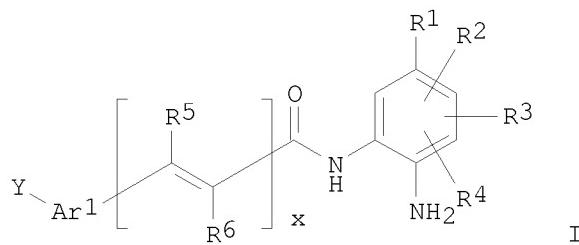
6

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/513699

L14 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:300394 CAPLUS
DOCUMENT NUMBER: 142:373563
TITLE: Preparation of amide derivatives as inhibitors of histone deacetylase
INVENTOR(S): Moradei, Oscar; Paquin, Isabelle; Leit, Silvana;
Frechette, Sylvie; Vaisburg, Arkadii; Besterman,
Jeffrey M.; Tessier, Pierre; Mallais, Tammy C.
PATENT ASSIGNEE(S): Methylgene, Inc., Can.
SOURCE: PCT Int. Appl., 389 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|--|---|---|
| WO 2005030704 | A1 | 20050407 | WO 2004-US31590 | 20040924 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG | | | | |
| JP 2008094847 | A | 20080424 | JP 2007-281356
US 2003-505884P
US 2003-532973P
US 2004-561082P
JP 2006-528279 | 20071030
P 20030924
P 20031229
P 20040409
A3 20040924 |
| PRIORITY APPLN. INFO.: | | | | |
| OTHER SOURCE(S): GI | | CASREACT 142:373563; MARPAT 142:373563 | | |



AB Title compds. I [Ar1 = (un)saturated-, (un)substituted-mono or fused poly-cyclic hydrocarbyl optionally containing 1-4 heteroatoms per ring; R1 = (un)substituted-mono-, -bi-, -tri-cyclic-aryl or -heteroaryl; R2, R3, and R4 independently = H, halo, amino, etc.; R5 and R6 independently = H, alkyl, aryl, etc.; x = 0-1; Y = any pharmaceutically acceptable chemical moiety consisting of 1 to 50 atoms with provisions] and their pharmaceutically acceptable salts, are prepared and disclosed as inhibitors of histone deacetylase. Thus, e.g., II was prepared by Suzuki coupling of 2-bromo-2-nitro-phenylamine (preparation given) with 2-thiopheneboronic acid followed by carbonylation with 4-[3,4-dimethoxy-(phenylamino)-methyl]benzoic acid (preparation given) and subsequent reduction. The inhibitory

capability of I towards antiproliferative activity of histone deacetylase enzyme was evaluated using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay and it revealed that certain compds. of the invention had MTT IC₅₀ values in the range of below 1 up to 20 μM. I as histone deacetylase inhibitors should prove useful in the treatment of diseases such as, but not limited to, cell proliferative disease, protozoal disease, and fungal disease.

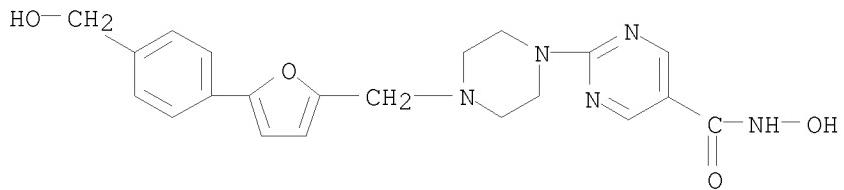
IT 603985-86-0P 603985-88-2P 603985-90-6P
603985-94-0P 603991-95-3P 603991-96-4P
603992-24-1P 603992-25-2P 603992-26-3P
603992-27-4P 603992-28-5P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

RN (preparation of amide derivs. as inhibitors of histone deacetylase)
603985-86-0 CAPLUS

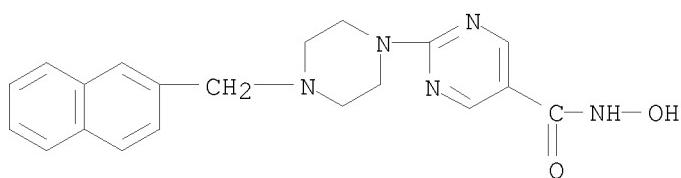
10/513699

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl- (CA INDEX NAME)



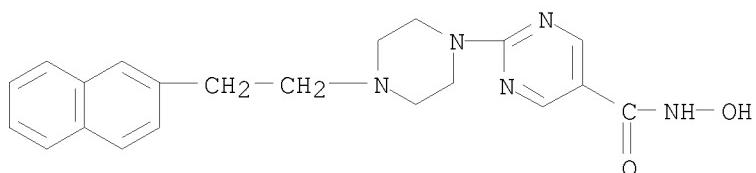
RN 603985-88-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl- (CA INDEX NAME)



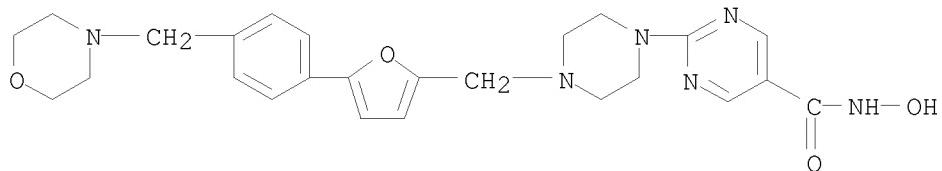
RN 603985-90-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl- (CA INDEX NAME)



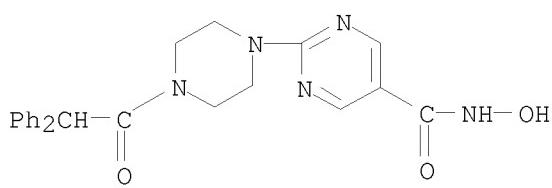
RN 603985-94-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl- (CA INDEX NAME)



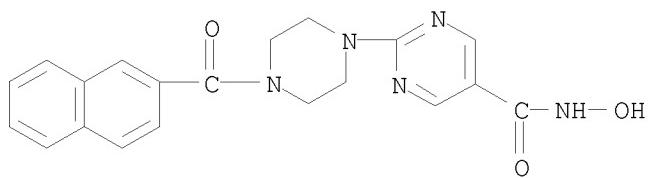
RN 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



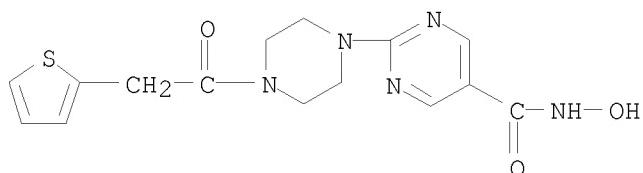
RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



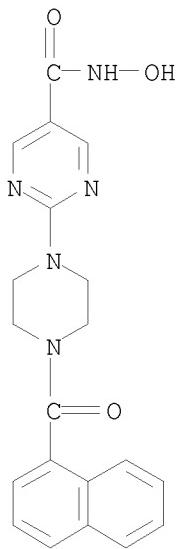
RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)

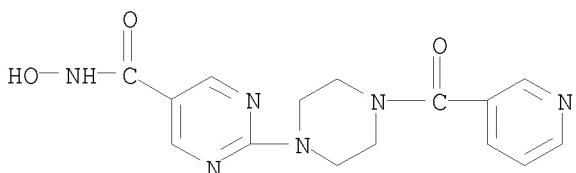


RN 603992-25-2 CAPLUS

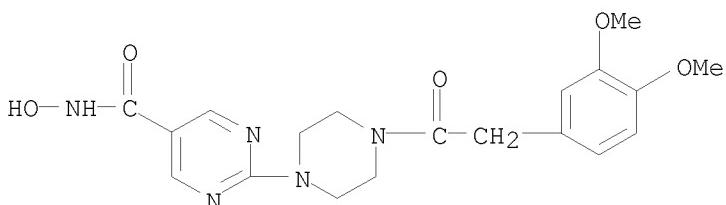
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



RN 603992-26-3 CAPLUS
 CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

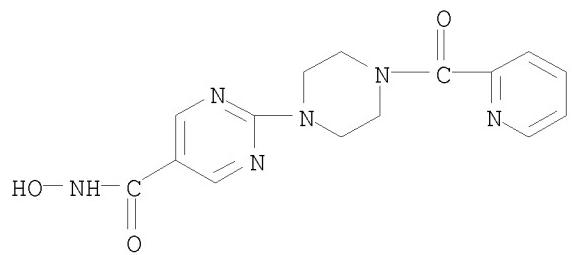


RN 603992-27-4 CAPLUS
 CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



RN 603992-28-5 CAPLUS
 CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

10/513699



REFERENCE COUNT:

6

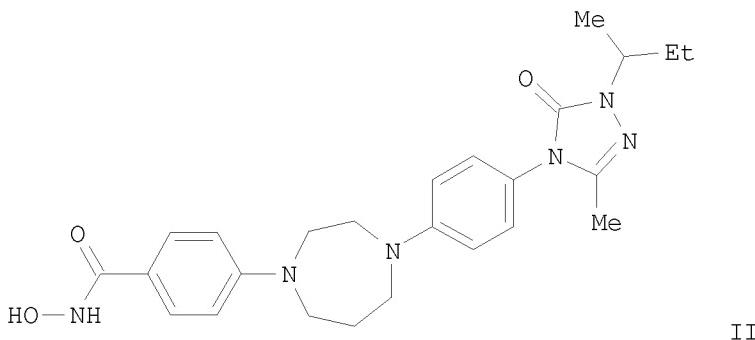
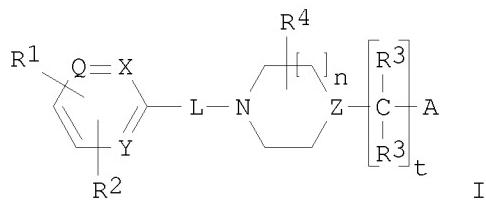
THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN
 ACCESSION NUMBER: 2003:737723 CAPLUS
 DOCUMENT NUMBER: 139:261309
 TITLE: Preparation of N-hydroxy-5-piperazino(piperidino or diazepino)-2-pyrimidinecarboxamides and N-hydroxy-4-piperazino(piperidino or diazepino)benzamides as new inhibitors of histone deacetylase
 INVENTOR(S): Angibaud, Patrick Rene; Pilatte, Isabelle Noeelle Constance; Van Brandt, Sven Franciscus Anna; Roux, Bruno; Ten Holte, Peter; Verdonck, Marc Gustaaf Celine; Meerpoel, Lieven; Dyatkin, Alexey Borisovich Janssen Pharmaceutica N.V., Belg.
 PATENT ASSIGNEE(S):
 SOURCE: PCT Int. Appl., 72 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 8
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|-------------|
| WO 2003076400 | A1 | 20030918 | WO 2003-EP2514 | 20030311 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2475764 | A1 | 20030918 | CA 2003-2475764 | 20030311 |
| AU 2003218736 | A1 | 20030922 | AU 2003-218736 | 20030311 |
| EP 1485353 | A1 | 20041215 | EP 2003-711980 | 20030311 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| BR 2003008081 | A | 20041221 | BR 2003-8081 | 20030311 |
| CN 1639125 | A | 20050713 | CN 2003-805675 | 20030311 |
| CN 1642551 | A | 20050720 | CN 2003-805833 | 20030311 |
| NZ 534834 | A | 20050729 | NZ 2003-534834 | 20030311 |
| JP 2005526067 | T | 20050902 | JP 2003-574621 | 20030311 |
| CN 101007803 | A | 20070801 | CN 2007-10005212 | 20030311 |
| IN 2004DN02533 | A | 20070413 | IN 2004-DN2533 | 20040831 |
| US 20050107384 | A1 | 20050519 | US 2004-506998 | 20040908 |
| ZA 2004007237 | A | 20050928 | ZA 2004-7237 | 20040909 |
| ZA 2004007235 | A | 20051004 | ZA 2004-7235 | 20040909 |
| ZA 2004007232 | A | 20051006 | ZA 2004-7232 | 20040909 |
| ZA 2004007233 | A | 20051006 | ZA 2004-7233 | 20040909 |
| ZA 2004007234 | A | 20051006 | ZA 2004-7234 | 20040909 |
| ZA 2004007236 | A | 20051006 | ZA 2004-7236 | 20040909 |
| MX 2004PA08806 | A | 20041126 | MX 2004-PA8806 | 20040910 |
| NO 2004004194 | A | 20041001 | NO 2004-4194 | 20041001 |
| PRIORITY APPLN. INFO.: | | | US 2002-363799P | P 20020313 |
| | | | WO 2002-EP14833 | A 20021223 |
| | | | CN 2003-805921 | A3 20030311 |

OTHER SOURCE(S):
GI

MARPAT 139:261309



AB The title compds. [I; n = 0-3; t = 0-4; Q, X, Y = N, C; Z = N, CH; R1 = CONR7R8, NHCOR9, CO(alkanediyl)SR9, etc. (wherein R7, R8 = H, OH, alkyl, etc.; R9 = H, alkyl, alkylcarbonyl, etc.); R2 = H, halo, OH, etc.; L = a bond, alkanediyl, alkanediyoxy, NH, CO, NHCO; each R3 = H and one H atom can be replaced by aryl; R4 = H, OH, NH2, etc.; A = (un)substituted Ph, cyclohexyl, pyridyl, etc.], having histone deacetylase inhibiting enzymic activity, were prepared and formulated. E.g., a multi-step synthesis of II which showed pIC50 of 5.121 against HDAC, was given.

IT 603985-87-1P 603985-89-3P 603985-91-7P
603985-95-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of piperazino(piperidino or diazepino) substituted 2-pyrimidinecarbohydroxamic acids and N-hydroxybenzamides as new inhibitors of histone deacetylase)

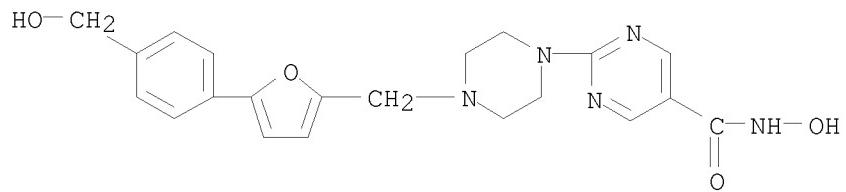
RN 603985-87-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

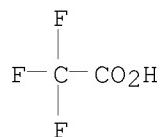
CRN 603985-86-0
CMF C21 H23 N5 O4

10/513699



CM 2

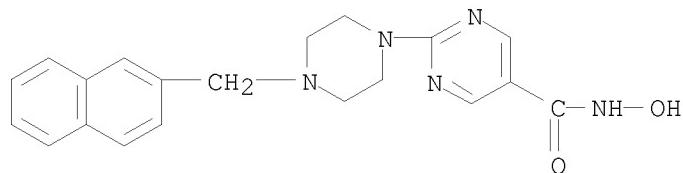
CRN 76-05-1
CMF C2 H F3 O2



RN 603985-89-3 CAPLUS
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

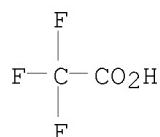
CM 1

CRN 603985-88-2
CMF C20 H21 N5 O2



CM 2

CRN 76-05-1
CMF C2 H F3 O2



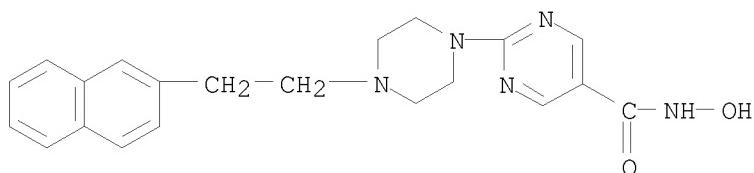
RN 603985-91-7 CAPLUS

10/513699

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

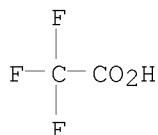
CM 1

CRN 603985-90-6
CMF C21 H23 N5 O2



CM 2

CRN 76-05-1
CMF C2 H F3 O2

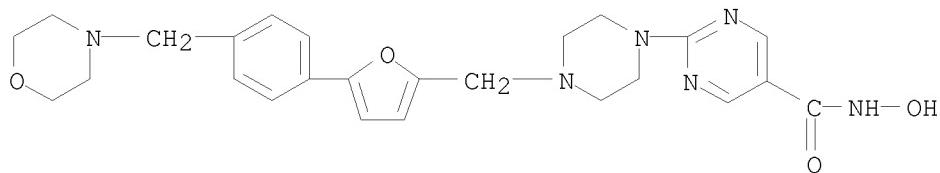


RN 603985-95-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl-, 2,2,2-trifluoroacetate (1:2) (CA INDEX NAME)

CM 1

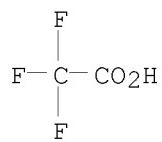
CRN 603985-94-0
CMF C25 H30 N6 O4



CM 2

CRN 76-05-1
CMF C2 H F3 O2

10/513699



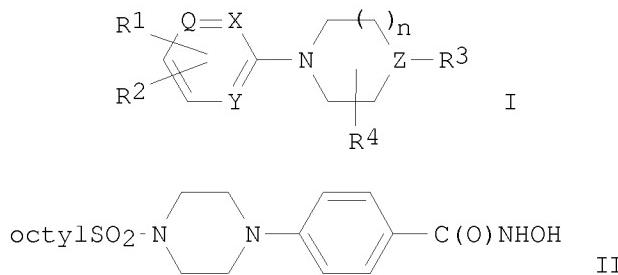
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN
 ACCESSION NUMBER: 2003:737586 CAPLUS
 DOCUMENT NUMBER: 139:261308
 TITLE: Preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases
 INVENTOR(S): Van Emelen, Kristof; Verdonck, Marc Gustaaf Celine; Van Brandt, Sven Franciscus Anna; Angibaud, Patrick Rene; Meerpoel, Lieven; Dyatkin, Alexey Borisovich Janssen Pharmaceutica N.V., Belg.
 PATENT ASSIGNEE(S):
 SOURCE: PCT Int. Appl., 52 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 8
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|-------------|
| WO 2003075929 | A1 | 20030918 | WO 2003-EP2515 | 20030311 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2476065 | A1 | 20030918 | CA 2003-2476065 | 20030311 |
| AU 2003218737 | A1 | 20030922 | AU 2003-218737 | 20030311 |
| AU 2003218737 | B2 | 20080410 | | |
| EP 1485099 | A1 | 20041215 | EP 2003-711981 | 20030311 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| BR 2003007624 | A | 20050111 | BR 2003-7624 | 20030311 |
| CN 1639125 | A | 20050713 | CN 2003-805675 | 20030311 |
| CN 1642551 | A | 20050720 | CN 2003-805833 | 20030311 |
| JP 2005525379 | T | 20050825 | JP 2003-574203 | 20030311 |
| NZ 534832 | A | 20050930 | NZ 2003-534832 | 20030311 |
| CN 101007803 | A | 20070801 | CN 2007-10005212 | 20030311 |
| IN 2004DN02537 | A | 20070112 | IN 2004-DN2537 | 20040831 |
| ZA 2004007237 | A | 20050928 | ZA 2004-7237 | 20040909 |
| ZA 2004007235 | A | 20051004 | ZA 2004-7235 | 20040909 |
| ZA 2004007232 | A | 20051006 | ZA 2004-7232 | 20040909 |
| ZA 2004007233 | A | 20051006 | ZA 2004-7233 | 20040909 |
| ZA 2004007234 | A | 20051006 | ZA 2004-7234 | 20040909 |
| ZA 2004007236 | A | 20051006 | ZA 2004-7236 | 20040909 |
| MX 2004PA08797 | A | 20041126 | MX 2004-PA8797 | 20040910 |
| US 20050096468 | A1 | 20050505 | US 2004-507785 | 20040913 |
| NO 2004004113 | A | 20040928 | NO 2004-4113 | 20040928 |
| PRIORITY APPLN. INFO.: | | | US 2002-363799P | P 20020313 |
| | | | WO 2002-EP14833 | A 20021223 |
| | | | CN 2003-805921 | A3 20030311 |
| | | | WO 2003-EP2515 | W 20030311 |

OTHER SOURCE(S): MARPAT 139:261308

GI



AB This invention comprises aryl and heteroaryl hydroxamic acids (shown as I; variables defined below; e.g. II) having histone deacetylase inhibiting enzymic activity; their preparation, compns. containing them and their use as a medicine. Compds. I show excellent in-vitro histone deacetylase inhibiting enzymic activity, have advantageous properties with regard to cellular activity and specific properties with regard to inhibition of cell cycle progression at both G1 and G2 checkpoints (p21 induction capacity), and show good metabolic stability and high bioavailability and more particular show oral bioavailability. They can also be used for detection and identification of histone deacetylase. General synthetic procedures and characterization data for twenty-seven I are included; also, preps. of 12 intermediates are included. For example, a 59 % yield of 2-[4-(dimethylaminosulfonyl)piperazin-1-yl]pyrimidine-5-carbohydroxamic acid was obtained by removing the O-tetrahydropyranyl group of its ester using trifluoroacetic acid; the ester was prepared in 61 % yield from N'-(ethylcarbonimidoyl)-N,N-dimethyl-1,3-propanediamine monohydrochloride, sodium 2-[4-(dimethylaminosulfonyl)piperazin-1-yl]pyrimidine-5-carboxylate, O-(tetrahydro-2H-pyran-2-yl)hydroxylamine, and 1-hydroxy-1H-benzotriazole in CH₂Cl₂/THF. The sodium salt was obtained by base hydrolysis of the Et ester; the ester was prepared in 73 % yield from Et 2-(piperazin-1-yl)pyrimidine-5-carboxylate and dimethylsulfamoyl chloride; Et 2-(piperazin-1-yl)pyrimidine-5-carboxylate was obtained in <96 % yield from Et 2-(4-benzylpiperazin-1-yl)pyrimidine-5-carboxylate by hydrogenation using Pd/C; the benzyl derivative was obtained from 1-(phenylmethyl)piperazine, (135 mL) was added gradually to a solution of potassium carbonate (0.18 mol) and 2-(methylsulfonyl)-5-pyrimidinecarboxylic acid Et ester, K₂CO₃ in MeCN. For I: n is 0-3; Q, X and Y are N or C; Z is N or CH; R1 is -C(O)NR5R6, -N(H)C(O)R7, -C(O)-C1-6alkanediylSR7, -NR8C(O)N(OH)R7, -NR8C(O)C1-6alkanediylSR7, -NR8C(O)C:N(OH)R7 or another Zn-chelating-group; R2 is H, halo, hydroxy, amino, nitro, C1-6alkyl, C1-6alkyloxy, trifluoromethyl, di(C1-6-alkyl)amino, hydroxyamino or naphthalenylsulfonylpnazinyl. R3 is H, C1-6-alkyl, arylC2-6alkenediyl, furanylcarbonyl, naphthalenylcarbonyl, -C(O)phenylR9, C1-6alkylaminocarbonyl, aminosulfonyl, arylaminosulfonyl, aminosulfonylamino, di(C1-6-alkyl)aminosulfonylamino, arylaminosulfonylamino, aminosulfonylaminoc1-6-alkyl, di(C1-6-alkyl)aminosulfonylaminoc1-6-alkyl, arylaminosulfonylaminoc1-6alkyl, di(C1-6-alkyl)aminoC1-6alkyl, C11-12-alkylsulfonyl, di(C1-6-alkyl)aminosulfonyl, trihaloC1-6-alkylsulfonyl, di(aryl)C1-6alkylcarbonyl, thiophenylC1-6alkylcarbonyl, pyridinylcarbonyl or arylC1-6alkylcarbonyl. R4 is H, hydroxy, amino, hydroxyC1-6alkyl, C1-6alkyl, C1-6alkyloxy,

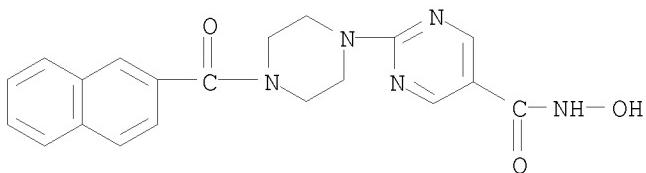
arylC1-6alkyl, aminocarbonyl, hydroxycarbonyl, aminoC1-6-alkyl, aminocarbonylC1-6-alkyl, hydroxycarbonylC1-6-alkyl, hydroxyaminocarbonyl, C1-6-alkyloxycarbonyl, C1-6-alkylaminoC1-6-alkyl or di(C1-6-alkyl)aminoC1-6-alkyl; when R3 and R4 are present on the same C atom, R3 and R4 together may form -C(O)-NH-CH2-NR10- wherein R10 is H or aryl; when R3 and R4 are present on adjacent C atoms, R3 and R4 together may form :CH-CH:CH-CH: ; addnl. details are given in the claims.

IT 603991-96-4P
 RL: ARG (Analytical reagent use); PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate and reagent for detection/identification of histone deacetylase; preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases)

RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



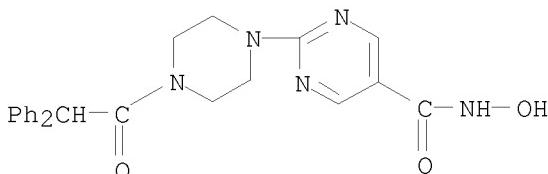
IT 603991-95-3P 603992-24-1P 603992-25-2P
 603992-26-3P 603992-27-4P 603992-28-5P

RL: ARG (Analytical reagent use); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate and reagent for detection/identification of histone deacetylase; preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases)

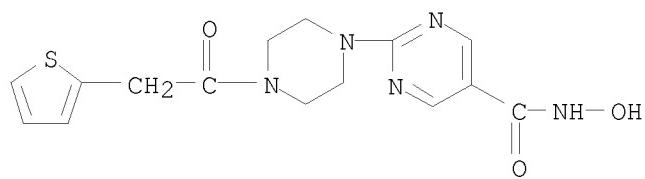
RN 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)



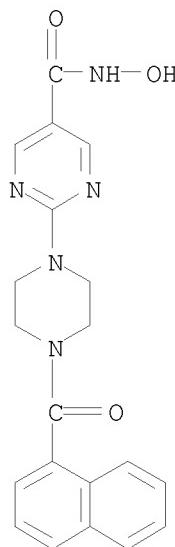
RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)



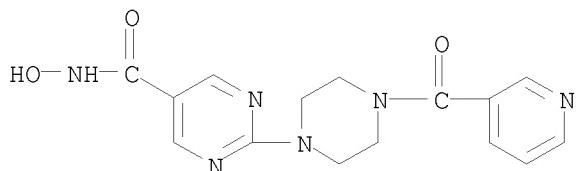
RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



RN 603992-26-3 CAPLUS

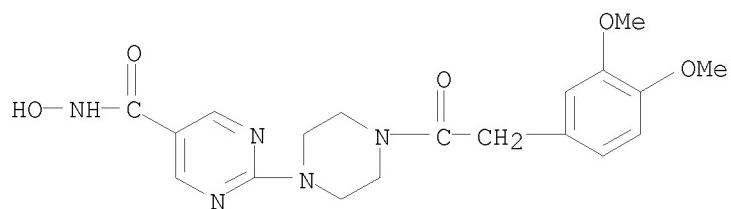
CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



RN 603992-27-4 CAPLUS

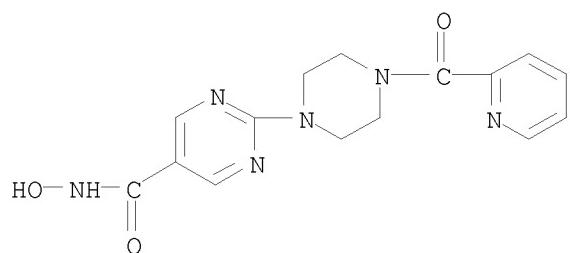
CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

10/513699



RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)



REFERENCE COUNT:

6

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/513699

=>
Connection closed by remote host